REMARKS

The foregoing amendments and these remarks are in response to the Office Action dated February 25, 2003. This amendment is filed with a request for a three month extension of time and authorization to charge Deposit Account No. 50-0951 for the extension of time. At the time of the Office Action, claims 1, 4-12, 14-17, 19-27, 30-33 and 37-51 were pending in the application.

I. Claim renumbering and amendments

Reconsideration of this Application and entry of the foregoing amendments are requested. Claims 1, 4-12, 14-17, 19-25, 27, 30-32, 36-44 and 47-51 have been cancelled and new claims 52-90 have been entered. Independent claims 52, 63, 64 and 75 recite a method to extract a total lipid fraction. Support for the amendments to these claims can be found, for example, at page 5, lines 5 to 7 and at page 8, lines 15 to 19. Further support for this terminology may be found throughout the disclosure where it is shown that the lipid fraction extracted from marine and aquatic animal is the total lipid fraction as may be seen more particularly in Table 13. Table 13 describes the various components of the lipids extracted according to the present claims which include triglycerides, free fatty acids, monoglycerides and phospholipids.

Claims 62, 63 and 64 do not recite "filleting-by-products". Support for this deletion may be found in the claims 15 and 16 as originally filed.

II. Rejections Under 35 U.S.C. § 103

The Office Action rejected claims 1, 4-12, 14-17, 19-25, 27, 30-32, 36-44, 47-51 under 35 U.S.C. § 103(a) as being unpatentable over the disclosures of CA 2,155,571, WO 8401715, JP 360035057A and US 6,055,936 ("Collins") taken as a whole.

Prior to discussing the rejections, a brief presentation on the nature and constituents of lipids including those of marine and aquatic animal lipids is provided.

Lipids from animal and plant tissues

Within its generally recognized meaning and within the meaning of that which is recited by the claims, the term "lipid" refers to naturally occurring substances soluble in organic solvents, but insoluble in water. The diverse groups of substances encompassed by this definition can be divided into two broad classes: the acyl lipids and the terpenoids (minor components). The acyl lipids may then be subdivided into further subclasses: neutral acyl lipids (glycerides, free fatty acids and cholesterol esters), and polar lipids including glycerophospholipids, glyceroglycolipids and sphingolipids. Terpenoids are comprised of two subclasses of minor components: the sterols and the chlorophylls and carotenoids. Carotenoids constitute a very minor constituent of lipids in marine animals. The Examiner is referred to Table 17 on page 29 of the present application providing the content in astaxanthin and canthaxanthin of fractions obtained and to page 10, lines 26 to 31 where it is indicated that the content of astaxanthin is about 75-124µg/g and the cont nt of canthaxanthin is about 250-700 µg/g. It is apparent throughout the present application that the term "total lipid" as used therein is meant to encompass all these various types of lipids and that the method of the present invention is able to extract all these various types of lipids.

Marine oils

The oils extracted from marine and aquatic materials can be separated into two types, according to their composition. The oils extracted from most fishes constitute the first oil type. It is composed of more than 90% of neutral acyl lipids, the major part of which are glycerides. Glycerides are fat reserves of marine animals. Cod liver oil for instance, is mostly constituted of glycerides.

The second oil type is composed of a lesser proportion of neutral acyl lipids and of glycerophospholipids, and sphingolipids. Krill lipids for instance may contain about 44% neutral acyl lipids (triglycerides, monoglycerides and free fatty acids) and about 54% of phospholipids (Phosphatidylcholines, Phosphatidylethanolamines, lysophosphatidylcholines

and phosphatidylserines) and sphingolipids (sphingomyelin) (see table 13 of the present application).

Prior to the present invention, the only solvents that appeared to produce good results to extract total lipids from krill was a combination of chloroform and methanol. Notably, however, these solvents are unacceptable for the food industry, because after their evaporation, some toxic residues could remain in the lipids. There is no reported success of total lipids extraction with non-toxic solvents generally recognized as safe (GRAS). Furthermore, although acetone was used to extract certain components of lipids, it was never disclosed to extract total lipids from marine and aquatic animals.

CA 2,155,571, JP 360035057A and Collin

It is respectfully submitted that JP 360035057A, Collin and CA 2,155,571, do not describe the use of acetone or ethanol for extracting "total lipids" within the meaning of the present application but to extract only a small fraction of total lipids, namely carotenoids for JP 360035057A and Collin, and polyunsaturated fatty acids for CA 2,155,571.

JP 360035057A and Collin teach that acetone is a conventional solvent for the recovery of fatty acids and lipid pigments (astaxanthin and canthaxanthin) of marine animals. Both polyunsaturated fatty acids and pigments constitute minor components of marine animal lipids. In the present application, the fraction 1 is a lipid fraction extracted with acetone according to a specific embodiment of the present invention. Analysis of lipid classes shows that free fatty acids constitute about 23.7% (See table 13) of total lipids of that fraction. The pigments, found in the hydrocarbon group (see Table 13) are only present as trace. As may further be seen from Table 17 of the present application, pigments constitute 0.0364% of the total lipid extracts of krill obtained according to the present invention (i.e. 93.1+270.4 =363.5µg/g oil). It is therefore submitted that techniques such as those described in JP 360035057A and Collin, which are able to extract less than 25% of total lipids, cannot be considered to be methods for total lipid extraction.

It is also respectfully submitted that it was not predictable from references such as those describing the extraction of minor components of marine animal lipids, namely

polyunsaturated fatty acids and lipid pigments with acetone, that the remaining major components of lipids could also be extracted from marine animal with acetone. None of the cited references JP 360035057A, Collin or CA 2,115,571 disclose or suggest that acetone can efficiently extract glycerides, glycerophospholipids and sphingolipids from marine animals.

Notably, the cited prior art teaches away from using acetone to extract glycerophospholipids, sphingolipids and glycerides. Dawson et al., *Textbook of RMC*, Third Ed. "Data for Biochemical Research" and *The Merck Index*, 12th edition, Budavari et al., Ed. Merck Research Laboratories, 1996 teach that phosphatidylethanolamines, sphingomyelin and phosphatidylcholine are practically insoluble in acetone and that phosphatidylserine and lysophosphatidylcholine are only slightly soluble in acetone. The Table below presents the solubility of various glycerophospholipids and sphingolipids in acetone as disclosed in these references. Please find enclosed copies of the rel vant extracts of these references.

Lipid	Reference	Solubility
Phosphatidylcholine (lecithin)	Dawson p.181	slightly soluble in acetone soluble in ethanol
	Merck #5452, p.925	insoluble in acetone partially soluble in ethanol
Phosphatidylethanolamines (cephalin)	Dawson p.181	insoluble in acetone soluble in ethanol
	Merck #2022, p.328	insoluble in acetone slightly soluble in ethanol
Phosphatidylserines	Dawson p.183	insoluble in acetone insoluble in ethanol
Phosphatidylinositol	Dawson p.183	insoluble in acetone insoluble in ethanol
Sphingomyelin (sphingosine)	Dawson p.184	insoluble in acetone insoluble in ethanol
	Merck #8899, p.1495	insoluble in acetone insoluble in ethanol

It is also noteworthy that acetone is not mentioned as a potential solvent for triglycerides and that many of these neutral lipids are indicated to be only slightly soluble in ethanol. It is therefore respectfully submitted that at the time of the Applicants' invention, th prior art taught away from using acetone as a solvent for extracting lipids from marine animal. The Applicants themselves fortuitously discovered acetone's potential as a solvent for the extraction of krill lipids while they were investigating for a means to dehydrate krill tissues. In summary, the prior art does not disclose or suggest that the main classes of lipids (glycerophospholipids, sphingolipids and glycerides) can be efficiently extracted with acetone or ethanol.

Destruction of main components of krill lipids

JP 360035057A discloses an process by which krill is combined with an organic solvent such as acetone or hexane and a lipase. The main process seeks to decompose glycerides and phospholipids into fatty acids in order to achieve the concentration of carotenoids which can then be utilized as a dye. Now, as indicated earlier, marin and aquatic animals lipids contain glycerides, free fatty acids, phospholipids, glyceroglycolipids and sphingolipids. Each of these components are constituted in part of fatty acids. Thus, the method of JP 360035057A would damage the major components of marine and aquatic animals lipids.

For medical, cosmetic and nutritional applications, it is advantageous to preserve marine lipid integrity because they are then more easily assimilated in the organism. Hence, phospholipids for instance contribute to the formation of an emulsion with triglycerides during digestion, thereby facilitating lipase action which in turn may progressively release fatty acids and enable their good absorption by the organism. Furthermore, many if not all components of the total lipid extracts have nutritional values. A method able to extract the total lipids is therefore advantageous.

WO 8401715

WO 8401715 describes a carbon tetrachloride (CCl_4) extraction of enzymes from water-extracted lipids (see page 10, lines 4 to 10 of WO 8401715). CCl_4 is toxic according to the Merck Index (#1864, page 297 Merck Index, 12th edition): it may cause liver and kidney damage and may be a carcinogen.

In stark contrast, the method of the present invention is directed to an extraction of total lipids of marine and aquatic animals with a ketone solvent or a mixture of a ketone and an ethanol solvent or ethyl acetate. According to a specific embodiment of the present invention, active enzymes may be recovered from the solid residues produced. WO 8401715 does not disclose or suggest a method for extracting total lipids from marin and aquatic animals with a ketone solvent, the solvent used in WO 8401715 for extracting lipids is CCl_4.

In view of the above and foregoing, withdrawal of the rejection under 35 U.S.C. §103, first paragraph is respectfully requested. The rejections of the original claims are believed to have been overcome by the present remarks and the introduction of new claims. From the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order, and such action is earnestly solicited.

III. Conclusion

Applicant has made every effort to present claims which distinguish over the prior art, and it is believed that all claims are in condition for allowance. Nevertheless, Applicant invites the Examiner to call the undersigned if it is believed that a telephonic interview would expedite the prosecution of the application to an allowance. In view of the foregoing remarks, Applicant respectfully requests reconsideration and prompt allowance of the p nding claims.

Respectfully submitted,

Date: 8-25-03

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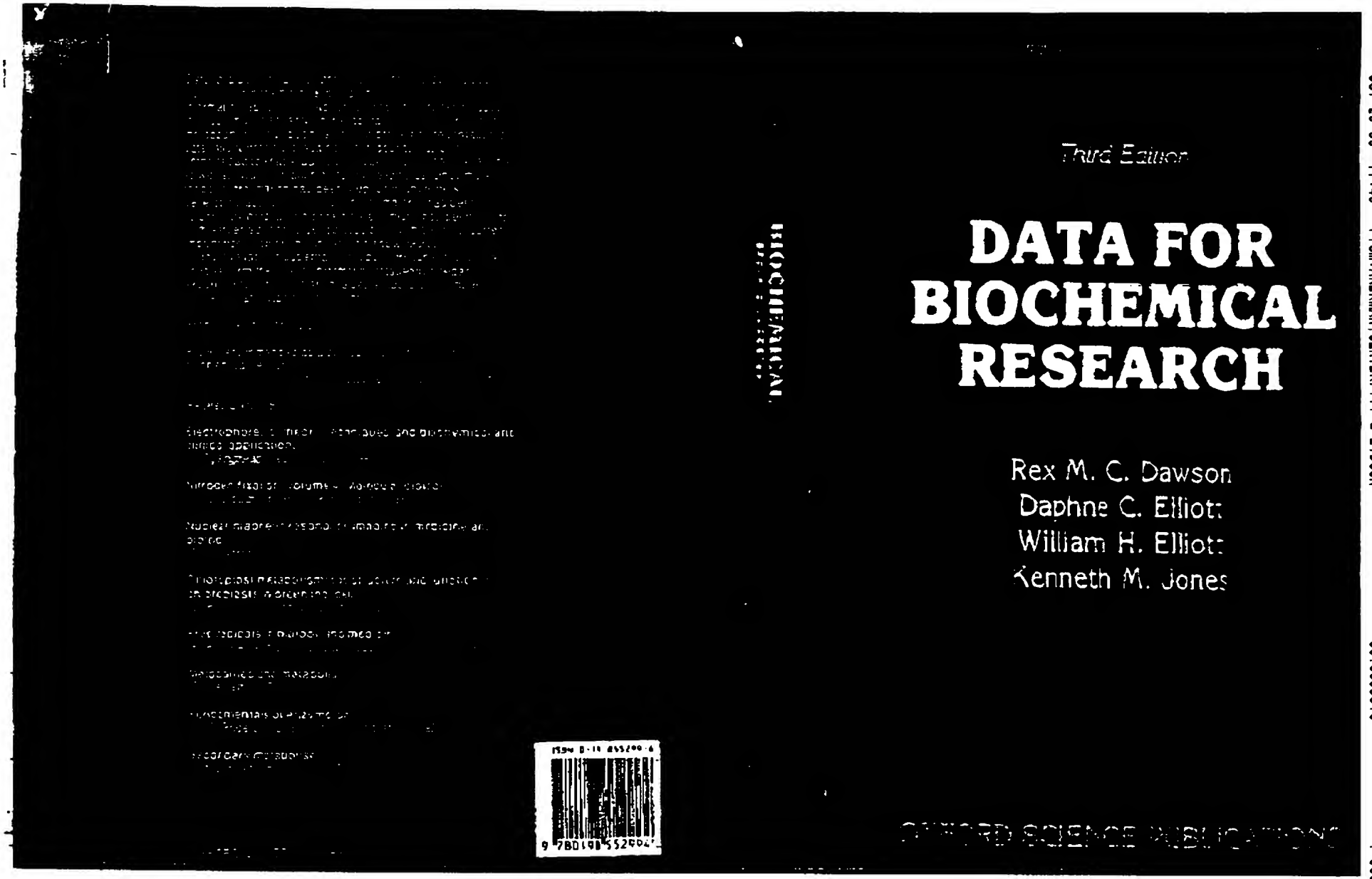

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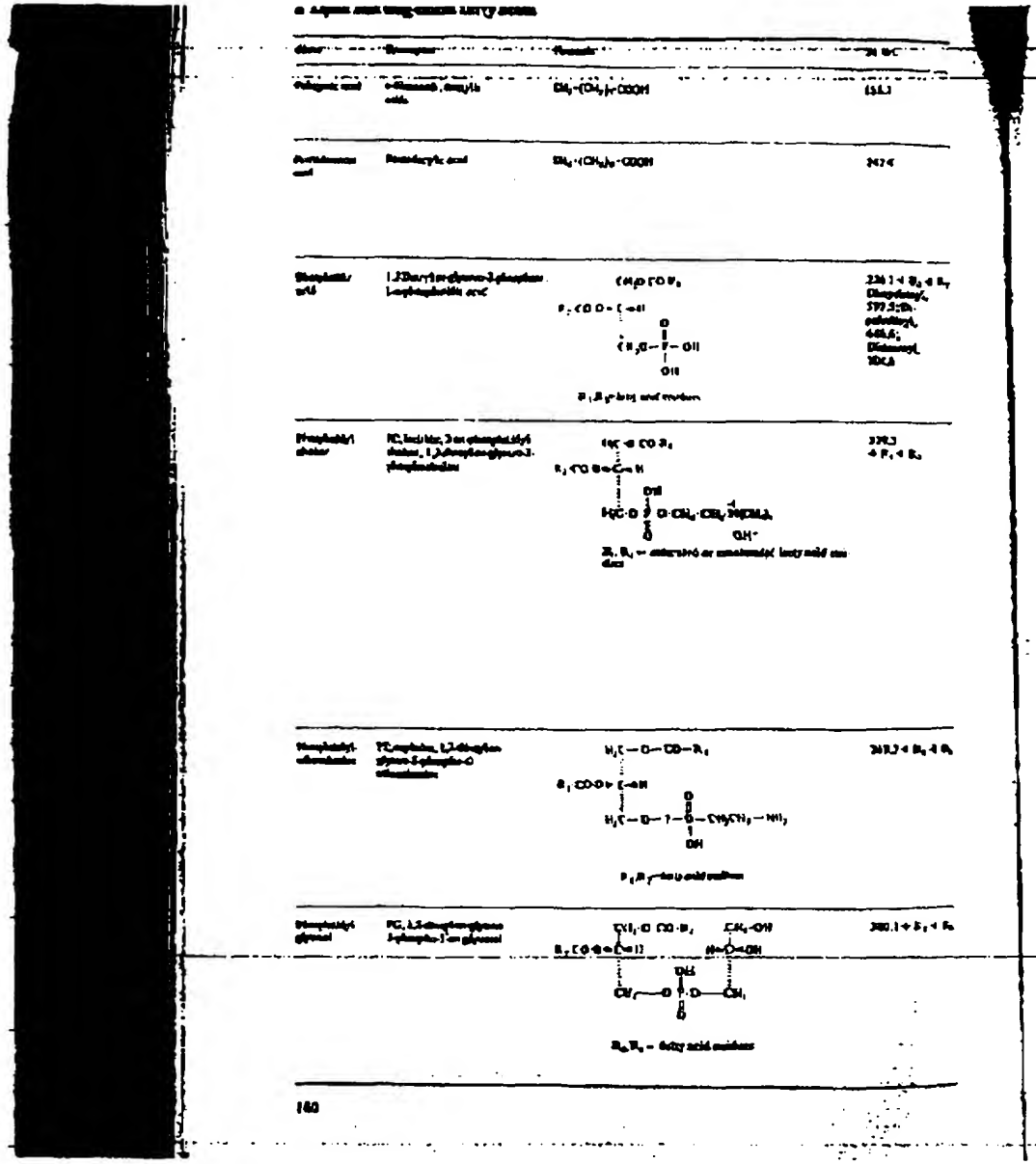
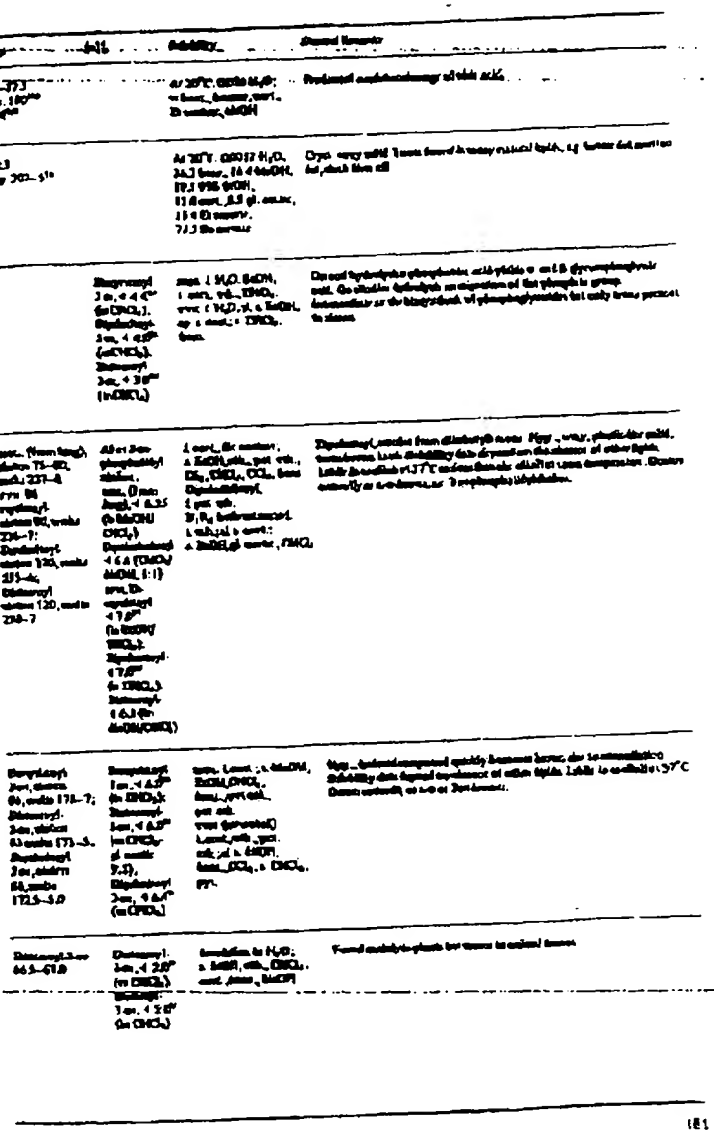
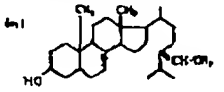
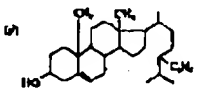
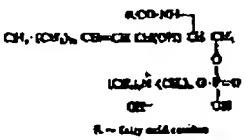
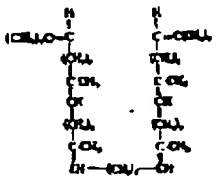




Name	Synonyms	Formula	M. wt.
Ricinoleic acid	12-Hydroxyoleic; (R)-cis-12-hydroxyoctadec-9-enoic acid; ricinolic acid	$CH_3(CH_2)_5CH(OH)CH_2CH{=}CH(CH_2)_7COOH$	298.5
Stigmasterol m.p. 169–170°	22-Dehydrositosterol; (22E)-24α-ethylcholesta-5,22-dien-3β-ol		412.7
	3,7,12-Trihydroxycholanoic; 3α,7α,12α-trihydroxy-5β-cholan-24-oic acid		410.6
Sphingomyelins	Choline phosphoceramides; N-acylsphingosine-1-phosphocholines	 R = fatty acid residue	692.8 + R
Sphingosines	4-Sphingenines; erythro-2-amino-1,3-dihydroxy-trans-4-octadecene	$CH_3(CH_2)_{12}CH{=}CHCH(OH)CH(NH_2)CH_2OH$	299.5
—sulphate		$C_{18}H_{37}NO_5H_2SO_4$	397.6
Squalene	Spinacene		410.7
Stearaldehyde	Octadecanal	$CH_3(CH_2)_{16}CHO$	268.5

Mp	[α]D	Solubility	General Remarks
45, 1-3 (pent; 57)	+4–4° (in ethanol)		Biosynthesis of ricinoleic acid from triglyceride of ricinoleic acid. Absolute configuration: see Chem. Ind. 1958, 1540.
164–6	+6.7° (in $CHCl_3$)	s. ± CH_2Cl_2, ±dil	m.p. 174° (dimethylformamide–EtOH). Usually in needles; gives blue-green test. Precipitated by digitonin. m. Fieser: Steroids, N.Y. 1959, 177. Shoppee, Ill.p. 177.
216–8	−11.8° (in $CHCl_3$)	s. ± $CHCl_3$	Isolated from soybean oil. Ill.p. 113–4. Shoppee, Ill.p. 163–6.
96–7 (108)	+6 to +10 (in $CHCl_3$/ MeOH)	s. alk., warm Et_2O; ± hexane, $CHCl_3$; hot EtOH; hot Et acetate	Wh. crys. Stable on incubation in aq. NaOH at 37° C but hydrolyses at higher temperatures. Hydrolysed in acid media; HCl_{aq} (100° C) yields phosphocholine and a basic sphingosylphosphocholine.
121–33	Free base, +5.5° (10 mg in 2ml pyr.)	s. H_2O; ± $CHCl_3$, CH_3OH, cold, alkalis.	Free base, needles from pet. eth.; fatty base, mixture of needles from EtOH; r. hygr. Trimethyl deriv., Ill.p. 101–2.
Sulphate, 248–52 (180–97)	Sulphate, −10.77° (in $CHCl_3$)	Sulphate; s. $CHCl_3$, hot EtOH containing H_2SO_4	
Squalene — 20 Bp 311°		s. alk., $CHCl_3$; sp. s. EtOH, gl. acetic	Col., oxidises air. Transmutation to cholesterol biosynthesis. Found in many animal tissues, but in appreciable quantity in some marine liver oils. Hexahydrochloride, Ill.p. 108–10, 144–5.
49.5 (16), polymorphic, very rapidly on W.p. crystallises		s. Et_2O; ± EtOH, eth, pet., alk., acid.	Amorphous wh. Can be formed from phenanthrene on cold hydrolysis. Polymerises very rapidly on keeping.

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A number of changes have been made since the Eleventh Edition was published in 1989. The monograph section has been extensively revised. The chemical structures have been redrawn employing current conventions for chemical depictions. Nomenclature has been reviewed and stereochemical descriptors have been added, where pertinent. In response to requests from our readership, the section on Organic Name Reactions, which last appeared in 1983 in the Tenth Edition, has been updated and reintroduced. The compilation of Chemical Abstracts Service Registry Numbers has been significantly expanded. Several new tables have been added including a glossary emphasizing some of the newer terminology employed in the fields of molecular biology and immunology.

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(London) 1961, 1468. R. W. Thompson in Kirk-Othmer *Encyclopedia of Chemical Technology* vol. 4 (Wiley-Interscience: New York, 3rd ed., 1978) pp 342-759

Highly reactive, volatile, very flammable liq. *Pentenes*: The general distillation cuts obtained are reported to have a sweet, pleasing, and ethereal odor, while the most unsaturated and reagent grades are said smelling. Do not standing has a long time. Burns with a blue flame to CO_2 and SO_2. *Acute fire and explosion hazard.* Can be ignited by hot electric pipes. Flash pt, closed cup, −10°. Ignition pt, 100°. Explosive range: 1 to 58% (v/v) in air. d_4^{20} 1.22921, d_4^{25} 1.27015, d_4^{30} 1.24812. Vapor sank to the ground. *Vapor density* 2.67 (air = 1). mp −111.8°, bp_{760} −73.1°, bp_{400} −44.7°, bp_{200} −31°, bp_{100} −16.8°; bp_{50} −6.1°; bp_{20} +9.2°; bp_{10} +18.5°. *Dry temp* 210.0°. *wet temp* 72.9 atm. n_D^{20} 1.43159, n_D^{25} 1.42823, n_D^{30} 1.42543. *Surface tension* at 20° 33.75. *Coefficient of viscosity* at 20° 0.343. *Heat of vaporization* at bp: 5.41 kcal/g. *Heat of fusion*: 1.949 kcal/mole. *Heat capacity* at 25°: 18.71 cal/mole/deg. Bruce, Mosher, *J. Am. Chem. Soc.* 59, 500 (1937). *Miscibility*: moderate. 2.35% Dielectric constant at low frequencies. 2.641. *Dipole moment*: 0.0. Soly in water at 20°: 0.204% Soly of water in CS_2: <0.0003%. *Azeotrope* with water bp 42.6°, contains 97.2% CS_2. Misc with anhydr methanol, ethanol, ether, benzene, chloroform, carbon tetrachloride, oils. Can be stored in iron, aluminum, glass, porcelain, Teflon.

Caution: Poisoning usually occurs from inhalation but also may be caused by ingestion and skin absorption. *Acute Toxicity*: euphoria, excitement, nervous convulsions, nausea, vomiting, unconsciousness, terminal convulsions. *Chronic Toxicity*: marked psychic disturbances ranging from extreme irritability to severe with hallucinations, tremors, auditory and visual disturbances, weight loss, blood dyscrasias. Dermal contact with cured skin may cause burning pain, erythema, exfoliation. *See Clinical Toxicology of Commercial Products*, R. E. Gosselin *et al.*, 5th (Williams & Wilkins: Baltimore, 4th ed., 1976) Section III, pp 83-86

Use: In the manufacture of rayon, carbon tetrachloride, trichloroacetic, and dithiocarbonic, electronic vacuum tubes. Solvent for phosphorus, sulfur, selenium, bromine, iodine, fats, resins, rubbers.

1860. Carbonic Anhydrase. *Carbonate dehydratase; carbonate hydro-lyase.* Mol wt ~30,000. A small enzyme (a zinc-type) which catalyzes the hydration of CO_2. Found in higher animals in erythrocytes, renal cortex, and gastric mucosa of mammals; also found in other animal tissues, in plant seed as some bacteria. Isolated from bovine erythrocytes. Lundsgaard, *Biochem Biophys Acta* 19, 218 (1940). Also from human erythrocytes: Nyman, *Acta* 13, 1 (1961), from renal cortex: Hibbs, *Proc. Soc Exp Biol Med* 49, 67 (1942), from gastric mucosa: Davenport, *Physiol Rev* 24, 560 (1944). Human carbonic anhydrase consists of two isoenzymes with distinctly different amino acid sequences and specific activities. The high activity form is called basic anhydrase C, the low activity form is called B, modified forms of these two isoenzymes exist. Fernandez-Deutsch, *J. Biol Chem* 243, 6474 (1968), 244, 3458 (1969). Amino acid sequence of carbonic anhydrase B. Anderson *et al.*, *Biochem Biophys Res Commun* 40, 692 (1970). Isol. Deutsch, *J Biol Chem* 248, 1825 (1973). sequence of carbonic anhydrase C. Henderson, Henriksson, *Biochem Biophys Res Commun* 57, 1308 (1974), Lin, Deutsch, *J. Biol Chem* 249, 2378 (1974). Crystal structure of carbonic anhydrase C. Liljas *et al.*, *Nature New Biol* 235, 131 (1972). Catalyzes the reversible reaction of CO_2 and H_2O to HCO_3^- and H^+. Provides CO_2 interchange between blood and tissues. In gastric mucosa, catalyzes role in sediment to neutralize the excess alkalinity produced by the secretions of water and excretion of hydrogen ion. Vaughan, Clark in *The Enzymes* vol. 2, part 2, J. B. Sumner, K. Myrbäck, Eds. (Academic Press, New York, 1951) pp 1253-1265. In the kidney, participates in Na^+ transport. Review of physiology. Review in *Oxygen Affinity of Hemoglobin and Red Cell Acid Base Status, Alfred Benzon Symposium IV*, P. Astrup, M. Rørth, Eds. (Academic Press, New York, 1972) pp 416-423. Review of metal ion function: Prince, Woolley, *Angew Chem Int Ed* 11, 408-417 (1972). *Review*: Lindskog *et al.*, "Carbonic Anhydrase" in *The Enzymes* vol. 4, P. D. Boyer, Ed. (Academic Press: New York, 1971) pp 587-665.

1861. Carbon Monoxide. CO, mol wt 28.01, C 42.85%, O 57.13%. Produced on an industrial scale by partial oxidation of hydrocarbon gases from natural gas or by the gasification of coal and coke. Conveniently prepd in the laboratory by heating calcium carbonate with Zn dust, Whitehouse, *J. Am Chem Soc.* 39, 447 (1948), by dehydration of formic acid with H_2SO_4: Gilliland, Blanchard, *Inorg Syn* 2, 61 (1946). Purification of carbon monoxide bought in steel cylinders: A. Klemenc, *Die Behandlung und Reinigung von Gasen* (Vienna, 1954) p 160. Glemser in *Handbook of Preparative Inorganic Chemistry* vol. 1, G. Brauer, Ed. (Academic Press, New York, 2nd ed., 1963); p 644. Review of toxic effects in humans. Stewart, *Ann Rev Biochem* 39, 409-426 (1970). Review C. M. Beckish, G. M. Brissel in Kirk-Othmer *Encyclopedia of Chemical Technology* 3rd ed. vol. 4 (Wiley-Interscience, New York, 3rd ed., 1978) pp 772-797.

Highly poisonous, odorless, colorless to violet gas. Very flammable, burns in air with a bright blue flame. Ignites in air, 700°. *bp* −205.0°. *bp* −191.5°. d_4^{-205} (liq) 0.814, d (gas) 0.968 (air = 1.000). d_4^0 at 760 mm: 1.250 g/liter. The gas pressure is 1500 psi. Flammable limits in air: 12.5 to 74 vol %. Crit pressure 35 atm, crit temp −139°. Heat capacity at 25°: 6.95 cal/mole/°C. Heat value per mol: 3013.8 kcal. Heat of formation −26.39 kcal/mol. Dec into carbon and carbon dioxide between 400 and 700°, at more temp when in contact with catalyst: sudanese. Above 800° the equilibrium reaction favors CO formation. Hopcalite, a mixture of the oxides of manganese and copper, catalyzes the decomp at room temp, as does Pd on silica gel. Sparingly sol in water: 3.3 ml/100 ml H_2O at 0°, 2.3 ml/100 ml H_2O at 20°. Freely absorbed by ammoniacal soln of cuprous chloride in HCl or in NH_4OH. Appreciably sol in some organic solvents, such as ethyl acetate. $CHCl_3$, acetic acid. The only important *and ethanol* is about 7 times as great as the soly in water.

Caution: Combines with the hemoglobin of the blood to form carboxyhemoglobin, which is useless as an oxygen carrier. *The symptoms*: Headache, mental dullness, dizziness, weakness, nausea, vomiting, loss of muscular control, increased then decreased pulse and respiratory rate, collapse, unconsciousness, death. *Antidote*: Oxygen. *See Patty's Industrial Hygiene and Toxicology* vol. 2C, G. D. Clayton, F. E. Clayton, Eds. (Wiley-Interscience: New York, 3rd ed., 1981) pp 4114-4124.

Use: As reducing agent in metallurgical operations especially in the blast process for the recovery of nickel, in organic synthesis especially in the Reppe-Trapsch process for petroleum-type products and in the oxo reaction in the manuf of metal carbonyls.

1862. Carbon Nitride. C_2N_2, mol wt 52.04. C 38.48%, N 60.68%. Cyanide; crystalline solid which exists in two forms, α and β. β-form may be built from distorted Model of structure and hardness. A. V. Lee, N. L. Cohen, *Science* 245, 841 (1989). Synthesis: E. E. Hall *et al.*, PCT Int. pat. Appl. WO 16,196, aidem, U.S. pat. 4,780,479 (1991), 1992 both to Regents U. California, Berkeley). C. Mu *et al.*, *Science* 261, 334 (1993). Hardness evaluation: D. Fukunaga, *Kagaku to Kogyo* 46, 321 (1992). *CA* 119, 245784 (1993).

1863. Carbon Suboxide. *1,3-Propadienedione; 1,3-dioxo; tricarbon dioxide.* C_3O_2, mol wt 68.03. C 52.96%, O 47.04%. O=C=C=C=O. Prepn by thermal decomp of malonic acid: Gürtzen in *Handbook of Preparative Inorganic Chemistry* vol. 2, G. Brauer, Ed. (Academic Press, New York, 2nd ed., 1963) p 645. Reactions in organic synthesis: Diels-Alder, *Ann Chem Rev* 24, 391 (1967). Comprehensive review: Reynolds, *Keto. Chem Rev* 7, 177 (1980); Vollhardt-Shen, *Angew Chem* 4, 610 (1935); Gomes, *Chimia* 38, 11 (1984); T. Kappe, E. Ziegler, *Angew. Chem Int Ed* 13, 491-504 (1974), reprinted in *New Synthetic Methods* vol. 3 (Verlag Chemie, Weinheim, 1985) pp 29-69.

Colorless, highly refractive liquid or colorless gas which burns with a blue, sooty flame. Odor like carbonic acid and unpleasant. mp −111.3°. bp_{760} 6.8°. d_4^0 1.114. n_D^0 1.45384. n_D^{20} 1.44337. Vapor pressure at 0° 357-389 mm. Explosive limits: 6 to 30 vol % in air. Dipole moment: 0.7D. Thermodynamic constants: Thompson, *Trans Faraday Soc* 57, 249 (1961). Though can be stored at pressures of up to 100 psig, but even at these pressures polymerization may occur, giving a red, water-sol product. Thus reasonably secure at higher pressures or in the liquid state. Polymerization initiated by pressures of P_2O_5. Dec when passed through heated glass tubes, forming a mirror surface. Dissolves in sol in carbon disulfide, xylene. With water forms carbonic and quantitatively. Forms malonamide with ammonia.

Caution: In small amounts acts as a lacrimator, in high amounts attacks eyes most, respiratory organs, producing a feeling of suffocation.

Use: Preps of malonates, improving dye affinity of fibers.

1864. Carbon Tetrachloride. *Tetrachloromethane; perchloromethane; Necatorina; Benzinoform.* CCl_4; mol wt 153.82. C 7.81%, Cl 92.19%. Obtained from carbon disulfide and chlorine in presence of a catalyst, e.g., $SbCl_3$, Fe filings or by the chlorination of hydrocarbons. Fields, Kryger & Clark's *Industrial Chemicals*, F. A. Lowenheim, M. K. Moran, Eds. (Wiley-Interscience: New York, 4th ed., 1975) pp 730-735. H. D. Dellow in Kirk-Othmer *Encyclopedia of Chemical Technology* vol. 5 (Wiley-Interscience: New York, 3rd ed., 1979) pp 704-714. Toxicity data: Smyth, *J. Ind Hyg. Toxicol* 29, 387 (1947), E. Browning, *Toxicity and Metabolism of Industrial Solvents* (Elsevier: New York, 1965) pp 173-188. Use in production of experimental liver disease: P. Traverso, A. P. Mezzoni, *Br J Exp Pathol* 46, 25 (1965). Review of carcinogenic risk: *IARC Monographs* 20, 371-399 (1979), ed toxicity studies: R. O. Rowland *et al.*, *Pharmacol Ther.* 43, 139-154 (1989).

Colorless, clear, nonflammable, heavy liquid, characteristic odor. May form phosgene when used to put out electrical fires. *Use only when adequate ventilation is provided.* d_4^{25} 1.589, bp_{760} 76.7°, mp −23°, n_D^{20} 1.4601. Can dissolve rubber, resin, wax with alcohol, benzene, chloroform, ether, carbon disulfide, gasoline, oils. LC_{50} in rats: 9526 ppm (Switzerly). LD_{50} on rats, mice, dogs (g/kg): 2.82, 11.8-14.4, 2.3 orally; LD_{50} on mice (g/kg): 4.1 ip, 20.4 sc. (IARC, 1979).

Caution: Poisoning may occur by inhalation, ingestion or skin absorption. *Acute*: exposure to high concentrations results in depression of the central nervous system manifested as loss of consciousness, dizziness, vertigo, headache, depression, mental confusion, incoordination, and gastrointestinal disturbances such as nausea, vomiting, abdominal pain and diarrhea. Acute exposure may result in renal damage leading to anuria and azotemia, and liver injury. Chronic: associated with liver and kidney damage. Skin contact can lead to dermatitis through defatting action. Inhalation may cause pulmonary edema and alveolitis. Concurrent intake with significant amounts of alcohol increases probability of injury. *See Patty's Industrial Hygiene and Toxicology* vol. 2B, G. D. Clayton, F. E. Clayton, Eds. (Wiley-Interscience: New York, 3rd ed., 1981) p 3472-3478; *Clinical Toxicology of Commercial Products*, R. E. Gosselin *et al.*, Eds. (Williams & Wilkins: Baltimore, 5th ed., 1984) Section III, p 103-107. This substance may reasonably be anticipated to be a carcinogen. *Seventh Annual Report on Carcinogens* (PB85-105701, 1984) p 137.

Use: As solvent for oils, fats, lacquers, varnishes, rubber, resins, resins, starting material in manuf of organic compds, grain fumigant. Pharmaceutic aid (solvent). Formerly used as dry cleaning agent and fire extinguishing.

Therapeutic use: Formerly as anthelmintic (Nematodes).

Trade name entry: Anthelmintic.

1865. Carbon Tetrabromide. *Tetrabromomethane; Tetra.* CBr_4; mol wt 331.63. C 3.62%, Br 96.38%. Prepd from carbon or carbon monoxide and bromine: Vorl. *Inorg Syn* 2, 24 (1936); Simons, Block, *J. Am Chem Soc* 61, 2962 (1939). Review in *Handbook of Preparative Inorganic Chemistry* vol. 1, G. Brauer, Ed. (Academic Press, New York, 2nd ed., 1963) p 226. May also be prepd from SiC_4 + F_2: Prens, *Inorg Syn* 3, 178 (1950).

Colorless, odorless gas. Thermally stable. Chemically very inert. d liquid, −195°) 1.98. d (liq, −183°) 1.89. mp −63.6°. bp −177°. May be stored in steel cylinders.

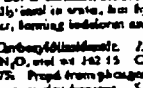
Caution: Narcotic in high concn.

Use: Low temp refrigerant, gaseous insulator.

1866. Carbon Tetraiodide. *Tetraiodomethane.* CI_4; mol wt 519.63. C 2.31%, I 97.69%. Prepd by the interaction of carbon tetrachloride and aluminum or calcium iodide: Gustavson, *Ann* 172, 173 (1874), boron iodide: Meerum, *Compt Rend* 113, 19 (1891), lithium or calcium iodide: Lantzsch, *ibid* 156, 1365 (1913)), ethyl iodide in the presence of aluminum chloride: Walter, *J Chem Soc* 85, 1090 (1904). Modification: Sergeev, *Inorg Syn* 3, 37 (1950).

Red cubic crystals. Odor of iodine. Dec to iodine and tetraiodoethylene under the influence of light or heat. d_4^{20} 4.32, mp 171°. Sol in benzene, chloroform. Dec by hot alcohol. Practically insol in water, but hydrolyzes slowly in contact with water, forming iodoform and iodine.

1867. *N,N'*-Carbonyldiimidazole. *1,1'-Carbonylbis-1H-imidazole.* $C_7H_6N_4O$, mol wt 162.15. C 51.85%, H 3.73%, N 34.55%, O 9.87%. Prepd from phosgene and imidazole in dry tetrahydrofuran or dry benzene: Staab, *Ann* 609, 75 (1957). Anderson, Paul, *J. Am Chem Soc* 80, 4423 (1958).



Crystals from tetrahydrofuran or benzene, mp 119.5-121°. Should be handled under conditions of atmospheric moisture. Hydrolyzed by water in a few sec with evolution of CO_2.

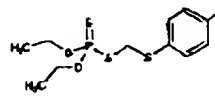
Use: In the synthesis of peptides. Reacts readily with carboxylic acids to form acyl imidazoles, subsequent reaction with amines to form amides. *Less* insecticidal.

1868. Carbonyl Fluoride. *Carbonic difluoride, fluorophosgene.* CF_2O, mol wt 66.01. C 18.20%, F 57.56%, O 24.24%. COF_2. Prepd from CO and F_2 or BrF_3, and CO: Ruff, Milchsäckly, *Z Anorg Allgem Chem* 231, 154 (1935). Research in *Handbook of Preparative Inorganic Chemistry*, vol. 1, G. Brauer, Ed. (Academic Press, New York, 2nd ed., 1963) p 206. Alternate route from CO + AgF_2: Fortlow *et al.*, *Inorg Syn* 6, 155 (1960).

Pungent, very hygroscopic gas. d (solid, −190°) 1.388. *d* (liq, −114°) 1.139, exp −114.0°, bp −83.1°. Heat of formation 166.6 kcal. Instantly hydrolyzes by water.

Caution: A strong irritant to skin, eyes, mucous membranes, respiratory tract.

1869. Carbophenothion. *Phosphorodithioic acid S-[[(4-chlorophenyl)thio]methyl] O,O-diethyl ester; S-[(p-chlorophenylthio)methyl] O,O-diethyl phosphorodithioate; O,O-diethyl S-(p-chlorophenylthiomethyl) phosphorodithioate; R-1303, Geschwister, Trithion.* $C_{11}H_{16}ClO_2PS_3$; mol wt 342.87. C 38.53%, H 4.70%, Cl 10.34%, O 9.33%, P 9.03%, S 26.06%. Prepn: Fancher, U.S. pat 2,780,226 (1957 to Geigy). Toxicity study: T. B. Gaines, *Toxicol Appl Pharmacol* 14, 515 (1969).

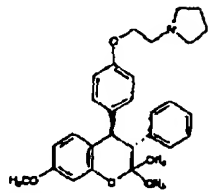


Light amber liquid. $bp_{0.01}$ 82°. d_4^{25} 1.271. n_D^{25} 1.5970, n_D^{30} 1.5950 (Fancher). Very low vapor pressure. Practically insol in water. Miscible with vegetable oils and most organic solvents. LD_{50} in female, male rats (mg/kg): 10, 10 orally; 27, 34 dermally (Gaines).

Caution: Cholinesterase inhibitor.

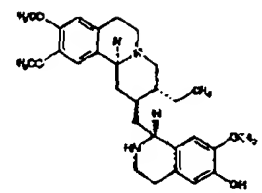
Use: Miticide; insecticide.

1870. Carbophenothion. *(SP-4-2)-Diethoxy[[4-(1,1-dimethylethyl)phenyl]thio]-1-methylethoxy; 1,1-dimethylethyl*



Crystals from ether/pet. ether, mp 99-100°, sublim ~50°. Hydrochloride, $C_{20}H_{24}NO_2$ HCl, 67/28 CDRH. White crystals, mp 165-166° (anhydrous). 737, 273 nm (ε 3700 at 273 nm). pKa 2.1. Sol in 40 parts chloroform, 20 parts acetone, 40 parts 95% ethanol, 20 parts methanol. Practically insol in water, isooctane, 0.1N HCl, 0.1N NaOH. LD_{50} ip in mice 440 mg/kg (Chal).

THERAP CAT: Antimalarial.



Needles from ether. Practically bitter taste. mp 115-118° $[\alpha]_D^{25}$ −61° (c = 1 in chloroform). Practically insol in water. Freely sol in dil hydrochloric acid, dil sulfuric and acetic acid, methanol, ethanol, acetone, chloroform. Less sol in ether, pet. ether.

Dihydrochloride heptahydrate: $C_{46}H_{62}Cl_2N_4O_{11}·7H_2O$, prisms, sinters at 245°, slowly melts up to 270° $[\alpha]_D^{25}$ −131° (c = 2). Sol in water. Solns have yellow color. Less sol in ethanol, chloroform. Practically insol in benzene, ligroin.

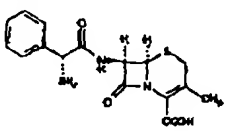
Dihydriodide acetate heptahydrate: $C_{46}H_{62}I_2N_4O_{11}·7H_2O$, prisms from dil hydriodic acid, sinters at 240°, slowly melts up to 255°. Sol in water, moderately sol in alcohol, acetone. Practically insol in benzene.

Methyl ether, see Ipecine.

THERAP CAT: Emetic, antiamebic.

THERAP CAT (vet.): Has been used as an emetic and as protozoacide.

2011. Cephalexin *[6R-[6α,7β(R*)]]-7-[(Aminophenylacetyl)amino]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid monohydrate; 7-(D-α-aminophenylacetamido)cephalosporanic acid monohydrate; 7-(D-2-amino-2-phenylacetamido)-3-acetoxymethyl-Δ³-cephem-4-carboxylic acid monohydrate; 7-(D-α-amino-α-phenylacetamido)-3-methyl-Δ³-cephem-4-carboxylic acid; 7-(D-α-amino-α-phenylacetamido)-3-(4-yellow prussiate)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid anxiolytic (other); 7-(D-2-amino-2-phenylacetamido)-3-acetoxymethyl-Δ³-cephem-4-carboxylic acid, 7-(D-α-amino-α-phenylacetamido) cephalosporanic acid, Ketaspore* $C_{16}H_{17}N_3O_4S$, mol wt 347.39. C 55.32%, H 4.93%, N 12.10%, O 18.42%, S 9.23%. Semisynthetic cephalosporin antibiotic. Preps: B. G. Morris, E. G. Jackson, U.S. pats. 3,275,626; 3,507,860 (1966, 1970 both to Lilly). Ryan *et al., J. Med. Chem.* 12, 300 (1969). Pharmacology and toxicology: Haggerty *et al., Ann. Rev. Ag. Chemother.* 1968, 353; Kind *et al., Wiener med. Mschr.* 161, 419. Comprehensive description: L. P. Hamilton, *Anal. Profiles Drug Subs.* 4, 21-46 (1975). Clinical pharmacology, efficacy, adverse reactions: *Postgrad. Med. J.* 48, Suppl. 3, 1-56 (1972).



Crystals or wax. 260 nm (ε 7250). pKa 5.2, 7.3

Monohydrate. *Cefadroxil, Cefamox, Ceporex, Duricef, Oracefal, Ospexin, Sefril, Sumizef, Ultracef, Cephaglycine, Sinacrose, Sumizef.* LD_{50} in mice, rats (g/kg): 1.6-4.5, > 5.0 orally, 0.4-1.7, > 3.2 ip (Wilcox)

Monohydrochloride: see hydrate, $C_{16}H_{17}N_3O_4S·HCl·H_2O$, *Keflet.*

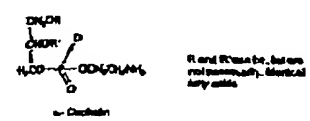
Sodium salt, $C_{16}H_{16}N_3NaO_4S$. *Alfaspore.*

Triclate salt: see Pivcefalexin.

THERAP CAT: Antibacterial.

THERAP CAT (vet.): Antibacterial.

2027. **Cephalins.** *Kephalins; phosphatidylethanolamines.* Group of phospholipids found in all living organisms. *Significant constituent of nervous tissue and brain extracts. Cephalins consist of glycerophosphoric acid in which the two free hydroxyls are esterified with long-chain fatty acid residues, and of hexahydric amino alcohol (as with the phosphoric group). α-Isomers are derivatives of α-glycerophosphoric acid, e.g.: β-isomers are derivatives of β-glycerophosphoric acid, e.g.: Natural products occur in the α-form, while the β-form is now recognized to be an artifact. Preps from mammalian "orphans brother": Rabinfeld, Portnoy, Biochem. Preps. 9, 5 (1957). U.S. pat. 2,801,255 (1957 to USDA). Diagnostic use: C. H. Rabin et al., Am. J. Gastroenterol. 56, 369 (1971). Review on natural and synthetic cephalins: E. Baer in Progress in the Chemistry of Fats and Other Lipids vol. 1, (MacMillan, New York, 1963) pp 39-44; Van Deenen, de Haas in Advances in Lipid Research, vol. 2 (Academic Press, New York, 1964) pp 183-189; Verkleij, Biol. Soc. Chim. Pharm. 1983, 1993.*



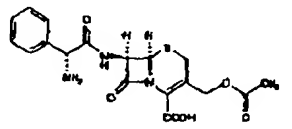
R and R' may be, but are not necessarily, identical fatty acids

Yellowish amorphous substance, characteristic odor and taste. Practically insol in water, acetone. Freely sol in chloroform, ether, slightly sol in ethanol.

USE: Clinical reagent (liver function test).

THERAP CAT: Hemostatic (local).

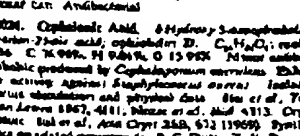
2032. **Cephaloglycin.** *[6R-[6α,7β(R*)]]-3-[(Acetyloxy)methyl]-7-[(2-thienylacetyl)amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid; 7-(2-amino-2-phenylacetamido)-3-(4-yellow prussiate)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid acetate (ester); 7-(D-2-amino-2-phenylacetamido)-3-acetoxymethyl-Δ³-cephem-4-carboxylic acid, 7-(D-α-amino-α-phenylacetamido) cephalosporanic acid, Ketaglycin* $C_{18}H_{18}N_3O_6S$, mol wt 405.43. C 53.33%, H 4.72%, N 10.36%, O 23.68%, S 7.91%. Semisynthetic cephalosporin antibiotic. Preps: Bldg. pat. 624,181, P. W. Wall *et al.*, U.S. pat. 3,422,103 (1964, 1969 both to Glaxo). Belg. pat. 1,017,620 (1966 to Merck & Co.). Aspects *et al., J. Med. Chem.* 9, 746 (1966), et al. and Dutcher Brit. pat. 965,747 (1965 to Lilly). Morris *et al., J. Antibiot. (A)*, 241 (1966). Metabolism and pharmacokinetics in man: I. Haggerty *et al., J. Antibiot.* 33, 230 (1980).



Dihydrate. *Keflex.* Crystalline powder. mp 253-256° (dec). ir max (in DMF): 251 nm (ε 11,300). Isoelectric point and pH of maximum stability: 4.5.

THERAP CAT: Antibacterial.

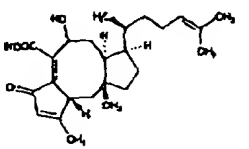
2034. **Cephalonium.** *[6R-[6α,7β(R*)]]-7-[(Aminophenylacetyl)amino]-3-[(carbamoyloxy)methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-(D-α-amino-α-phenylacetamido)-3-carbamoyloxymethyl-Δ³-cephem-4-carboxylic acid, Cefalonium* $C_{16}H_{18}N_4O_5S$, mol wt 378.41. C 50.78%, H 4.79%, N 14.81%, O 21.14%, S 8.47%. Semisynthetic cephalosporin antibiotic. Preps: Belg. pat. 624,181, P. W. Wall *et al.*, U.S. pat. 3,422,103 (1966, 1969 both to Glaxo). Belg. pat. 1,017,620 (1966 to Merck & Co.). Aspects *et al., J. Med. Chem.* 9, 746 (1966), et al. and Dutcher Brit. pat. 965,747 (1965 to Lilly). Morris *et al., J. Antibiot.* 33A, 241 (1966). Metabolism and pharmacokinetics in man: I. Haggerty *et al., J. Antibiot.* 33, 230 (1980).



Dihydrate. *Kefacon.* Crystalline powder. mp 273-276° (dec). ir max (in DMF): 251 nm (ε 11,300). Isoelectric point and pH of maximum stability: 4.5.

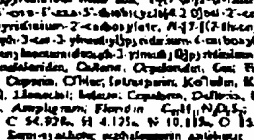
THERAP CAT: Antibacterial.

2036. **Cephalonium Acid.** *6-Hydroxy-3-acetoxymethyl-3,4-dihydro-2H-1,3-thiazine-4-carboxylic acid, cephalothin D.* $C_8H_{11}NO_6S$; mol wt 249.24. C 38.55%, H 4.45%, N 5.62%, O 38.51%, S 12.87%. Natural antibiotic metabolite produced by *Cephalosporium acremonium.* Exhibits weak activity against *Staphylococcus aureus.* Isolation, structure elucidation and physical data: Hou *et al., Tetrahedron Letters* 1967, 4811; Nozoe *et al., Ibid.* 4813. Crystal structure: Ikai *et al., Acta Cryst.* B28, 912 (1969). Synthetic studies on related compounds: P. C. Dutia, T. K. Dan, *Syn. Commun.* 6, 251 (1976), W. G. Dauben, D. S. Man, *J. Org. Chem.* 42, 912 (1977), R. K. Boeckman *et al., Ibid.* 3630.



Solid sol (19°, $[\alpha]_D$ +36.2° (c = 0.54 in chloroform) ir max: 250 nm (ε 11700).

2038. **Cephalonium.** *(6R-trans)-7-[[(7-Carboxy-8-oxo-7-[(2-(4-pyridinylthio)-3-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]pyridinium inner salt, 1-[(7'-β-[2-(4-thienyl)acetamido]-3'-oxo-5'-thia-1'-azabicyclo[4.2.0]oct-2'-en-3'-yl)-methyl]pyridinium-2'-carboxylate, R-[7-[(2-thienylacetamido)cephem-3-en-3-yl]methyl]pyridinium-4-carboxylate, N-[7-(2'-thienylacetamido)cephem-3-yl-methyl]pyridinium 2-carboxylate cephalaridan, Cutene, Cepalandan, Gen; Ferrolina; Caporan; Caporen, Other; Intrapoin, Keflodin, Kefloridin (chloride), Lilenacil; Indacef, Cepaloren, Duflorin, Keloporin, Lorefene, Amplagram; Flordin* $C_{19}H_{17}N_3O_4S_2$, mol wt 415.49. C 54.92%, H 4.13%, N 10.11%, O 15.40%, S 15.44%. Semisynthetic cephalosporin antibiotic. Preps: Fr. pat. 1,346,187 (1965 to Glaxo), C.A. 63, 11598c (1965), E. H. Flynn, U.S. pat. 3,498,988 (1969 to Lilly). Toxicity studies: Atkinson *et al., Toxicol. Appl. Pharmacol.* 8, 398 (1966).



Crystals. Soluble in water. Aq solns are slightly acid (pH 4.5-5). $[\alpha]_D$ +427° (c = 0.75 in water). ir max: 239, 257 nm (ε 15400, 13950). pKa 3.2. Aq solns (20% wt./vol.) are stable for four weeks at 4° in the dark. Exposure to sunlight causes discoloration. LD_{50} mice, rats (g/kg): > 15, 2.5-4 orally; in mice (g/kg): > 0.2 iv (Atkinson)

THERAP CAT: Antibacterial.

THERAP CAT (vet.): Antibacterial.

2035. **Cephalosporin C.** *[6R-[6α,7β(R*)]]-3-[(Acetyloxy)methyl]-7-[(5-amino-5-carboxy-1-oxopentyl)amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-(5-amino-5-carboxypentanamido)-3-hydroxymethyl-4-cephem-3-(1-carboxylate)-4.2.0]oct-2-ene-2-carboxylic acid acetate.* $C_{16}H_{21}N_3O_8S$; mol wt 415.42. C 46.26%, H 5.10%, N 10.12%, O 30.81%, S 7.72%. Antibiotic substance produced along with penicillin N by a *Cephalosporium* sp. cultivated from sea water and a sewage outfall on the coast of Sardinia. G. Brotzu, *Lav. Ist. Igiene Cagliari* (1948). Newton, Abraham, Nature 175, 548 (1955), *cadem. Biochem. J.* 63, 651 (1956), *cadem. Gen. pat.* 1,014,211 (1957 to Natl Res Dev Corp.), Brit. pat. 818,906 (1959), Kelly *et al., U.S. pat.* 3,085,085 (1963 to Natl Res Dev Corp.), Demain, U.S. pats. 3,184,374,77 (1965 to Merck & Co.). Biosynthesis: Demain, Newsbeke, *Appl. Microbiol.* 10, 321 (1962). Has the same side chain as penicillin N, but the nucleus is different and is named 7-aminocephalosporanic acid 7ACA, Hamby, *Eng. J. Pharmacol.* 16, 870 (1956). Brunner, Abraham, Newton, Biochem. J. 79, 377 (1961), Nadgir, Nandan, *Ibid.* 393. In cephalosporin C, the amino group is replaced by a pyrrolidinium group: Nair *et al., Ibid.* 403. Transformation to cephalosporin C, its salts, greatly activity is claimed Abraham *et al., U.S. pat.* 3,040,681 (1962 to Natl Res Dev Corp.). Total synthesis: Woodward *et al., J. Am. Chem. Soc.* 88, 852 (1966). Review of cephalosporin C and related compounds: Abraham, *Quart. Rev. Chem. Soc.* 21, 231 (1967). Abraham, Loder, in *Cephalosporins and Penicillins*, E. H. Flynn, Ed. (Academic Press, New York, 1972) pp 1-26.

water (g/100 ml): 0.057 (0°), 0.065 (20°). The only increases in the presence of HNO_3 or nitrates.

5426. **Lead Formate.** $C_2H_2O_4Pb$; mol wt 297.24. C 8.08%, H 0.68%, O 21.53%, Pb 69.71%. $Pb(CHO_2)_2$.
White, lustrous prisms or needles. *Poisonous!* d 4.63. Dec at 190°. Sol in 63 parts cold water, 6 parts boiling water; insol in alcohol.

5427. **Lead Hexafluorosilicate.** Lead fluosilicate; lead silicofluoride. F_6PbSi; mol wt 349.26. F 32.64%, Pb 59.32%, Si 8.04%. $PbSiF_6$.
Dihydrate, colorless crystals. Sol in water. *Poisonous!*
USE: In refining lead by electrolytic methods.

5428. **Lead Hydroxide.** Lead oxide hydrate; basic lead hydroxide. $H_2O_4Pb_3$; mol wt 687.61. H 0.29%, O 9.31%, Pb 90.40%. $3PbO.H_2O$. Prepn and structure: Oswald et al., *Helv. Chim. Acta* 51, 1389 (1968).
White powder, absorbs CO_2 from the air. *Poisonous!* d 7.41. Insol in H_2O; sol in dil acids, fixed alkali hydroxides.

5429. **Lead Hypophosphite.** $H_4O_4P_2Pb$; mol wt 337.18. H 1.20%, O 18.98%, P 18.37%, Pb 61.45%. $Pb(H_2PO_2)_2$.
Hygroscopic, cryst powder, dec at elevated temps. *Poisonous!* Slightly sol in cold water, more in hot water; insol in alcohol. *Keep well closed and protected from light.*

5430. **Lead Iodide.** I_2Pb; mol wt 461.01. I 55.06%, Pb 44.94%. PbI_2.
Bright yellow, heavy odorless powder. *Poisonous!* d 6.16. mp 402°. One gram dissolves in 1350 ml cold, 230 ml boiling water; sol in concd solns of alkali iodides; freely sol in soln of sodium thiosulfate; sol in 200 parts cold 90 parts hot aniline; insol in alcohol or cold HCl. *Protect from light.*
USE: Bronzing, gold pencils, mosaic gold, printing, photography.

5431. **Lead Lactate.** $C_6H_{10}O_6Pb$; mol wt 385.34. C 18.70%, H 2.62%, O 24.91%, Pb 53.77%. $Pb(C_3H_5O_3)_2$.
White, heavy, cryst powder. *Poisonous!* Slowly absorbs CO_2 from the air, becoming partly insol. Sol in water, hot alcohol. *Keep well closed.*

5432. **Lead Molybdate(VI).** MoO_4Pb; mol wt 367.14. Mo 26.13%, O 17.43%, Pb 56.44%. $PbMoO_4$. Occurs as the mineral *wulfenite*.
Yellow powder. Insol in water; sol in HNO_3 or NaOH when freshly pptd.
USE: In pigments.

5433. **Lead Monoxide.** Lead oxide yellow; plumbous oxide; litharge; massicot; lead protoxide. OPb; mol wt 223.20. O 7.17%, Pb 92.83%. PbO. Prepn of high purity PbO: Kwestroo, Huizing, *J. Inorg. Nucl. Chem.* 27, 1951 (1965); Kwestroo et al., *ibid.* 29, 39 (1967). Mfg processes: *Faith, Keyes & Clark's Industrial Chemicals*, F. A. Lowenheim, M. K. Moran, Eds. (Wiley-Interscience, New York, 4th ed., 1975) pp 509-513. Toxicity study: W. R. Bradley, W. G. Fredrick, *Ind. Med.* 10, *Ind. Hyg. Sect.* 2, 15 (1941).
Exists in two forms: red to reddish-yellow, tetragonal crystals, stable at ordinary temp; yellow, orthorhombic crystals, stable above 489°. Pauson, *J. Am. Chem. Soc.* 63, 2617 (1941). *Poisonous!* At 300-450° in the air, it converts slowly into Pb_3O_4, but at higher temp reverts to PbO. d 9.53. mp 888°. Insol in water, alcohol. Sol in acetic acid, dil HNO_3, in warm solns of fixed alkali hydroxides. LD_{50} i.p. in rats: 40 mg Pb/100g (Bradley, Fredrick).
Caution: Avoid breathing dust. Wear dust mask approved by U.S. Bureau of Mines for this purpose. Wash thoroughly before eating or smoking. Keep away from food or food products.
USE: In ointments, plasters, preparing salts of lead or basic salts. Glazing pottery, glass flux for painting on porcelain and glass, lead glass; varnishes, with glycerol as metal cement; producing iridescent colors on brass and bronze; coloring sulfur-containing substances, *e.g.*, hair, nails, wool, horn; mosaic artificial tortoise shell and horn; pigment for rubber, manuf boiled linseed oil, in assay of gold and silver ores.

5434. **Lead Nitrate.** N_2O_6Pb; mol wt 331.21. N 8.46%, O 28.98%, Pb 62.56%. $Pb(NO_3)_2$.
White or colorless translucent crystals. *Poisonous!* d 4.53. One g dissolves in 2 ml cold, 0.75 ml boiling water, in 2500 ml abs alcohol, 75 ml abs methanol; insol in concd HNO_3. The aq soln is slightly acid: pH of 20% aq soln at 25° = 3.0-4.0. USE: Match industry and explosives; pigments; as mordant in dyeing and printing on textiles; mordant for staining horn, mother-of-pearl; oxidizer in dye industry; sensitizer in photography; process engraving.
THERAP CAT (VET): Has been used as a caustic in equine practice.

5435. **Lead Oleate.** Oleic acid lead salt. Approx $Pb(C_{18}H_{33}O_2)_2$.
Granular, wax-like mass. Insol in water; sol when fresh in alc, benzene, ether, oil turpentine. LD orally in guinea pigs: 6.0 g/kg, *Handbook of Toxicology* vol. 1, W. S. Spector, Ed. (Saunders, Philadelphia, 1956) pp 176-177.
USE: In varnishes; in extreme pressure lubricants.

5436. **Lead Oxalate.** C_2O_4Pb; mol wt 295.22. C 8.14%, O 21.68%, Pb 70.19%.
White, heavy powder. Dec at 300°. d 5.28. *Poisonous!* Insol in water; sol in dil HNO_3, fixed alkali hydroxides; sparingly sol in acetic acid.

5437. **Lead Phosphate.** $O_8P_2Pb_3$; mol wt 811.51. O 15.77%, P 7.63%, Pb 76.59%. $Pb_3(PO_4)_2$.
White powder. d 6.9. mp 1014°. *Poisonous!* Insol in water, alcohol. Sol in HNO_3, fixed alkali hydroxides.
Note: This substance may reasonably be anticipated to be a carcinogen: *Seventh Annual Report on Carcinogens* (PB 95-109781, 1994) p 238.
USE: Stabilizer for styrene and casein plastics, in special glasses.

5438. **Lead Selenate.** O_4PbSe; mol wt 350.16. O 18.28%, Pb 59.17%, Se 22.55%. $PbSeO_4$. Prepd by adding a soln of lead nitrate to sodium selenate: Lenher, Kao, *J. Am. Chem. Soc.* 47, 1521 (1925).
Orthorhombic crystals. d 6.37. Dec by heat. Sol in concd acids; insol in water.

5439. **Lead Selenite.** O_3PbSe; mol wt 334.16. O 14.36%, Pb 62.01%, Se 23.63%. $PbSeO_3$. Prepd by adding selenious acid or an alkali selenite to a soln of lead chloride or nitrate: Berzelius, cited in Mellor vol. X, 833 (1930).
Powder. mp ~500°. Melts to a yellow liquid. Dec at a bright-red heat giving off selenium oxide. Very sparingly sol in water, difficultly dec by boiling sulfuric acid.

5440. **Lead Sesquioxide.** *Lead trioxide; plumbous plumbate.* O_3Pb_2; mol wt 462.40. O 10.38%, Pb 89.62%. Pb_2O_3.
Reddish-yellow powder; converted at 370° into Pb_3O_4, dec at ~530° to PbO. Insol in water, dec by concd HCl or H_2SO_4 with the liberation of Cl or oxygen, respectively.

5441. **Lead Sodium Thiosulfate.** Lead sodium hyposulfite. $Na_4O_9PbS_6$; mol wt 635.55. Na 14.47%, O 22.66%, Pb 32.60%, S 30.27%. $Na_4Pb(S_2O_3)_3$.
White, small, heavy crystals. *Poisonous!* Sparingly sol in water; react as thiosulfate solns.
USE: Manuf matches.

5442. **Lead Stearate.** Stearic acid lead salt. Approx $Pb(C_{18}H_{35}O_2)_2$.
White powder; mp ~125°. *Poisonous!* Insol in water; sol in hot alcohol.
USE: In extreme pressure lubricants, as drier in varnishes.

5443. **Lead Subacetate.** Lead monosubacetate; monobasic lead acetate. $C_4H_{10}O_8Pb_3$; mol wt 807.72. C 5.95%, H 1.25%, O 15.85%, Pb 76.96%. $Pb(C_2H_3O_2)_2.2Pb(OH)_2$.
White, heavy powder. *Poisonous!* Sol in 16 parts cold and 4 parts boiling water with alkaline reaction. On exposure to air absorbs CO_2 and becomes incompletely sol. *Keep well closed.*
USE: In sugar analysis, to remove coloring matters, etc. from solns before polarizing; for clarifying and decolorizing other solns of organic substances.

5444. **Lead Sulfate.** O_4PbS; mol wt 303.26. O 21.10%, Pb 68.32%, S 10.57%. $PbSO_4$. Occurs as the minerals *anglesite, lanarkite*.
White, heavy, cryst powder. *Poisonous!* d 6.2. mp 1170°. Sol in about 2225 parts water; more soluble in dil HCl or HNO_3, less in dil H_2SO_4; sol in NaOH, ammonium acetate or tartrate soln; sol in concd hydriodic acid; insol in alcohol. LD_{50} i.p. in guinea pigs: 290 mg/kg, *Handbook of Toxicology* vol. I, W. S. Spector, Ed. (Saunders, Philadelphia, 1956) pp 178-179.
USE: Instead of white lead as pigment; with zinc in galvanic batteries; metal treatment, in lithography, preparing rapidly drying oil varnishes; weighting fabrics.

5445. **Lead Sulfide.** PbS; mol wt 239.27. Pb 86.60%, S 13.40%. Occurs as the mineral *galena*. Toxicity study: W. R. Bradley, W. G. Fredrick, *Ind. Med.* 10, *Ind. Hyg. Sect.* 2, 15 (1941).
Black powder. Insol in water. Sol in HNO_3, hot dil HCl. LD_{50} i.p. in rats: 160 mg Pb/100 g (Bradley, Fredrick).
USE: Glazing earthenware.

5446. **Lead Telluride.** PbTe; mol wt 334.80. Pb 61.89%, Te 38.11%. Found in nature as the mineral *altaite*. Prepd from lead nitrate, sodium carbonate and powdered tellurium: Montignie, *Bull. Soc. Chim. France* 1947, 750. Prepn of single crystals by heating stoichiometric quantities of the elements in a graphite cup or fused quartz tube: Brady, *J. Electrochem. Soc.* 101, 466 (1954).
Silver-gray cubic crystals. d 8.16. mp 905°. Most of the crystal is p-type, the n-type material being present in the surface layer. Energy gap 0.27 ev. Electron mobility 2260 cm^2/volt-sec. Hole mobility 860 cm^2/volt-sec. Resistivity 0.003 ohm-cm (p type), 0.00390 ohm-cm (n-type). Not attacked by hydrochloric, hydrofluoric, perchloric and acetic acids or their mixtures; not attacked by solns of 30% potassium hydroxide or of alkali metal sulfides. Dil nitric acid turns the surface black, while concd nitric and perchloric lighten gray surface and turns the black surface to gray. Hot concd sulfuric acid produces a reddish-violet surface.
USE: In photoconductor cells, in semiconductor research.

5447. **Lead Tetraacetate.** $C_8H_{12}O_8Pb$; mol wt 443.38. C 21.67%, H 2.73%, O 28.87%, Pb 46.73%. $Pb(CH_3COO)_4$. Prepd from Pb_3O_4 and glacial acetic acid preferably in the presence of some acetic anhydride: Dimroth, Schweizer, *Ber.* 56, 1375 (1923); Bailar, *Inorg. Syn.* 1, 47 (1939); Brodersen in *Handbook of Preparative Inorganic Chemistry* vol. 1, G. Brauer, Ed. (Academic Press, New York, 2nd ed., 1963) p 767. Prepn by electrolysis: Proshin, Ostrikov, *Dokl. Akad. Nauk SSSR* 112, 303 (1957), *CA* 51, 16146 (1957); *et al.*, *Khim. Prom. (Moscow)* 46, 897 (1970), *CA* 74, 49800s (1971). Reviews of prepn and use as oxidizing agent: Criegee, "Oxidations with Lead Tetraacetate" in *Oxidation in Organic Chemistry*, Part A, K. B. Wiberg, Ed. (Academic Press, New York, 1965) pp 277-366; Zýka, *Pure Appl. Chem.* 13, 569-581 (1966).
Colorless monoclinic prisms from glacial acetic acid. Turns pink readily. Unstable in air. Hydrolyzed by water with the formation of brown lead dioxide and acetic acid. d 2.228. mp 175-180°. Sol in hot glacial acetic acid, benzene, chloroform, tetrachloroethane, nitrobenzene. Dissolves in concd halogen acids with the formation of haloplumbic acids, H_2PbX_6. The dry material can be stored in sealed, evacuated ampuls.
USE: Selective oxidizing agent in organic syntheses: Criegee, *Angew. Chem.* 53, 321 (1940); *Newer Methods of Preparative Organic Chemistry* (Interscience, N.Y., 1948) pp 1-17.

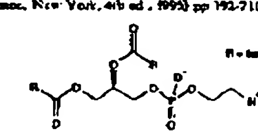
5448. **Lead Tetrafluoride.** Plumbic fluoride. F_4Pb; mol wt 283.19. F 26.83%, Pb 73.17%. PbF_4. Prepd by passing fluorine diluted with CO_2 or N_2 over PbF_2 at 300°: v. Wartenberg, *Z. Anorg. Allgem. Chem.* 244, 339 (1940). Review: Kemmitt, Sharp, *Advan. Fluorine Chem.* 4, 187 (1965).
White, tetragonal crystals; d 6.7. mp ~600°. Readily hydrolyzes and forms brown flakes (PbO_2) in the presence of moisture.
USE: Has been proposed as a fluorinating agent for hydrocarbons.

5449. **Lead Tetroxide.** Lead oxide red; red lead; minium; lead orthoplumbate; mineral orange; mineral red; Paris red; Saturn red; C.I. Pigment Red 105; C.I. 77578. O_4Pb_3; mol wt 685.60. O 9.33%, Pb 90.67%. Pb_3O_4. The article of commerce contains about 90% Pb_3O_4; the remainder being chiefly lead monoxide. Prepn: M. Baudler in *Handbook of Preparative Inorganic Chemistry* vol. 1, G. Brauer, Ed. (Academic Press, New York, 1963) pp 755-757. Structure: S. T. Gross, *J. Am. Chem. Soc.* 65, 1107 (1943). Review: *Mellor's* vol. 7 (1930) pp 672-680.
Bright-red, heavy powder. *Poisonous!* Dec at ~500° with evolution of oxygen. d 9.1. Insol in water or alcohol; sol in excess glacial acetic acid, in hot HCl with evolution of Cl, in dil HNO_3 in presence of H_2O_2. LD_{50} i.p. in guinea pigs: 220 mg/kg, *Handbook of Toxicology* vol. 1, W. S. Spector, Ed. (Saunders, Philadelphia, 1956) pp 176-177.
USE: Plasters and ointments, manuf colorless glass, glass for lenses, flux for porcelain painting, protective paint for iron and steel, oil-color for ship paints, vermilion; coloring rubber; cement for glass, gas and steam pipes, storage batteries, pencils for writing on glass, manuf lead peroxide, matches.

5450. **Lead Thiocyanate.** Lead sulfocyanate. $C_2N_2PbS_2$; mol wt 323.37. C 7.43%, N 8.66%, Pb 64.08%, S 19.83%. $Pb(SCN)_2$. Prepn: Goodrich, Wernberger, *Inorg. Syn.* 1, 85 (1939).
White, odorless powder. d 3.82. *Poisonous!* Sol in ~200 parts cold, 50 parts boiling water; also sol in alkali hydroxide and thiocyanate solns.
USE: Reverse dyeing with aniline black; manufacture of safety matches and cartridges.

5451. **Lead Vanadate(V).** Lead metavanadate. O_6PbV_2; mol wt 423.08. O 22.70%, Pb [illegible], V [illegible]. $Pb(VO_3)_2$.
Yellow powder. Insol in water. Dec by HNO_3.
USE: Manuf other vanadium compds; as pigment.

5452. **Lecithin.** Phosphatidylcholine; Lecithol; Vitellin; Kelecin; Granulestin. Phospholipid found in all living organisms (plants and animals). Significant constituent of nervous tissue and brain substance. A mixture of the diglycerides of stearic, palmitic, and oleic acids, linked to the choline ester of phosphoric acid. Commercial product contains 2.2% P. Isoln from eggs: Sinclair, *Can. J. Res.* 26B, 777 (1948). Product of commerce is predominantly soybean lecithin obtained as a by-product in the manuf of soybean oil: Stanley in K. S. Markley, *Soybeans* vol. II (Interscience, New York, 1951) pp 593-647. Soybean lecithin contains palmitic acid 11.7%, stearic 4.0%, palmitoleic 8.6%, oleic 9.8%, linoleic 55.0%, linolenic 4.0%, C_{20} to C_{22} acids (includes arachidonic) 5.5%. Synthesis of a mixed acid α-lecithin: de Haas, van Deenen, *Tetrahedron Letters* 1960 (no. 9), 1. Synthetic L-α-(distearoyl)lecithin is identical with hydrogenated egg yolk lecithin and L-α-(dipalmitoyl)lecithin is identical with ... palmitate, *i.e.*, a natural phosphatide of brain, lung, and spleen. Commercial grades of natural lecithin are reported to contain a potent vasodepressor substance: McQuarrie, Anderson, U.S. pat. 2,945,869 (1960 to Cutter Labs.). Comprehensive monograph: G. B. Ansell, J. N. Hawthorne, *Phospholipids* (Elsevier, New York, 1964) 439 pp; A. Wendel, "Lecithin" in *Kirk-Othmer Encyclopedia of Chemical Technology* vol. 15 (Wiley-Interscience, New York, 4th ed., 1995) pp 192-210.



R = fatty acids

Waxy mass when the acid value is about 20. Pourable, thick fluid when the acid value is around 30. Color is nearly white when freshly made, but rapidly becomes yellow to brown in air. d 1.0305. Iodine value 95, saponification

value 18. Insoluble but swells up in water and in reacts into forming a colloidal suspension. Soluble in about 12 parts acid, abs alcohol, and in chloroform, ether, pet ether, in mineral oils and fatty acids; sparingly sol in benzene, fixed mixtures; practically insol in cold vegetable and animal oils.

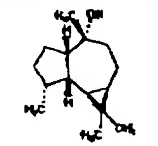
USE: Edible and digestible surfactant and emulsifier of natural origin. Used in margarine, chocolate and in the food industry in general. In pharmaceuticals and cosmetics. Many other industrial uses, e.g. treating leather and textiles.

THERAP CAT: Lipotropic.

5453. Lectins. Agglutinins; phytagglutinins; phytohemagglutinins, proteins. A group of proteins, widely distributed in nature, that have the ability to agglutinate erythrocytes and many other types of cells. Although their existence has been known since 1888, when Stillmark isolated a hemagglutinin from castor beans, the term "lectin" (from the Latin legere, to choose) was first introduced by W. C. Boyd and E. Shapleigh in Science 119, 419 (1954). It is now used to designate "a sugar-binding protein or glycoprotein of nonimmune origin which agglutinates cells and/or precipitates glycoconjugates". I. J. Goldstein et al., Nature 285, 66 (1980). Lectins are found primarily in seeds of plants, but also occur in roots, leaves and bark. In addition, they are present in invertebrates such as clams, snails, and horseshoe crabs, and in several vertebrate species. The term phytohemagglutinin is used to refer to plant lectins. Important members of the lectin family include concanavalin A, abrin, ricin, e.g.n. as well as soybean agglutinin or SBA and wheat germ agglutinin or WGA. Lectins vary considerably in chemical and physical properties, only a limited number have been purified. Mol wts of 17,000 to 400,000 have been reported and most lectins have been found to contain Mn^{2+} and Ca^{2+}. Nearly all lectins can be inhibited by free oligo- or monosaccharides of appropriate specificity. Although their physiological functions in plants or in other organisms are unknown, lectins exhibit a variety of unusual biological properties. Some are specific in their reactions with human blood groups; some induce mitosis in lymphocytes. WGA from wheat germ lipase has been shown to agglutinate various tumor cells more readily than cells from normal tissue. J. C. Aub et al., Proc. Nat. Acad. Sci. USA 50, 613 (1963); M. M. Burger, A. R. Goldberg, ibid. 57, 359 (1967). Soybean agglutinin and concanavalin A have been shown to agglutinate cell lines transformed by viral or chemical carcinogens: M. Inbar, L. Sachs, Nature 223, 710 (1969); eidem, Proc. Nat. Acad. Sci. USA 63, 1418 (1969); B. A. Sela et al., J. Membrane Biol. 3, 267 (1970). Some plant lectins mimic the direct effects of insulin on isolated rat adipocytes: phosphorylation: F. Pereira et al., Science 281, 467 (1983). Soybean agglutinin has also been used to form marrow transplants to patients with severe combined immunodeficiency. Y. Reisner et al., Blood 61, 341 (1983). Reviews: N. Sharon, H. Lis, Science 177, 949 (1972); eidem, Ann. Rev. Biochem. 42, 541-574 (1973); L. Sargent, Ann. Rev. Phytopathol. 14, 453-461 (1976). Book: Lectins: Biology, Biochemistry, Clinical Biochemistry vol. 1, T. C. Bøg-Hansen, Ed. (de Gruyter, New York, 1981) 414 pp.

USE: As tools for studying cell surface properties, in cancer research.

5454. Ledol. [1aR-(1aα,4aβ,7α,7aβ,7bα)]-Decahydro-1,1,4,7-tetramethyl-1H-cyclopropa[e]azulen-4-ol; "Ledum camphor". $C_{15}H_{26}O$; mol wt 222.37. C 81.02%, H 11.78%, O 7.19%. Occurs in the essential oil from leaves of Ledum palustre L.: Grassmann, Repert. Pharm. 38, 53 (1831); Hjelt, Ber. 28, 3087 (1895); from L. groenlandicum Oeder, L. columbianum Piper, Ericaceae: Oslo, Lyon, J. Am.

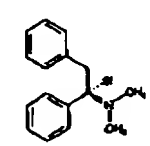


Chem. Soc. 48, 306 (1925). Structure: O. Motl et al., Tetrahedron Letters 1958 (no. 6), 14. Stereochemistry: L. Dolejs, F. Sorm, Tetrahedron Letters 1959 (no. 17), 1; stereochemistry: O. Motl et al., J. Am. Chem. Soc. 91, 6472 (1969).

Needles from alc, mp 104-105°. Sublimes easily, even below the mp. bp_{760} 292°. n_D^{20} 1.4667. $[\alpha]_D^{20}$ +28° (c = 10 in chloroform). Practically insol in water. Sol in alc (about 10% w/v). Soluble in other organic solvents.

Chromatic. $C_{15}H_{26}O$, ruby-red prisms, mp 97°. $[\alpha]_D$ +30° (c = 3 in chloroform).

5455. Lefetamine. (R)-N,N-Dimethyl-α-phenylbenzeneethanamine; (−)-1-N,N-dimethyl-1,2-diphenylethylamine; (−)-N,N-dimethyl-α-phenylphenethylamine. $C_{16}H_{19}N$; mol wt 225.32. C 85.29%, H 8.50%, N 6.22%. Centrally acting analgesic with structural resemblance to morphine. Prepn and activity: K. Ogiu et al., J. Pharm. Soc. Japan 80, 283 (1960); eidem, Japan. pat. 20,067('64) (to Res. Found. Practical Life). Absolute configuration: M. Nakazaki, Chem. & Ind. (London) 1962, 1577. NMR data indicate 37% eclipsed conformation which appears to enhance the selectivity for morphine receptors: T. Suzuki et al., J. Med. Chem. 9, 647 (1966). Pharmacology: H. Takagi, N. Shimizu, Arch. Int. Pharmacodyn. Ther. 221, 105 (1976). Clinical study: J. P. Rasmussen; T. L. Peters, Brit. Med. J. 21 (1979). Analgesic activity: M. Nozaki et al., Life Sci. 32, Suppl. 1, 431 (1983). Opioid agonist activity: M. Gonzalo de Miguel et al., Pharmacol. Res. Commun. 17, 471 (1985).



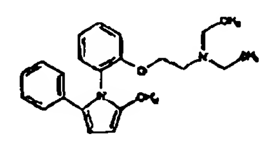
bp_{1} 147-147°. $[\alpha]_D^{20}$ −124.7° (ethanol).

Hydrochloride. $C_{16}H_{19}N.HCl$. Santenol, SPA. mp 211-219°. $[\alpha]_D^{20}$ −91.7° (water).

THERAP CAT: Analgesic.

5456. Leghemoglobin. Legoglobin. Hemoglobin-like red pigment present in the root nodules of leguminous plants. Isolation from soy beans: Keilin, Wang, Nature 155, 227 (1945); Appleby, Biochim. Biophys. Acta 60, 226 (1962). Mol wt is approx one-fourth that of hemoglobin. Ehrenberg, Ellfolk, Acta Chem. Scand. 17, S343 (1963). Resolved into four components on DEAE-cellulose column. Ellfolk, ibid. 14, 609 (1960). Suggested to act as an oxidation-reduction catalyst in the symbiotic nitrogen fixation. Abel, ibid. 15, 173 (1961). Primary structure of soybean leghemoglobin: Ellfolk, Sievers, ibid. 25, 3532 (1971).

5457. Leiopyrrole. N,N-Diethyl-2-[2-(3-methyl-5-phenyl-1H-pyrrol-1-yl)phenoxy]ethanamine; 1-[o-(2-diethylaminoethoxy)phenyl]-3-methyl-5-phenylpyrrole; 2-methyl-1-(2-β-diethylaminoethoxyphenyl)-5-phenylpyrrole. DP-714. $C_{23}H_{28}N_2O$; mol wt 348.49. C 79.27%, H 8.10%, N 8.04%, O 4.59%. Preparation: Buu-Hoi et al., J. Med. Pharm. Chem. 1, 23 (1959).



Base, $bp_{0.1}$ 252°. n_D^{20} 1.6025.

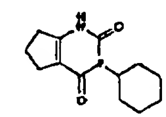
hydrocarbon tetrachloride, mp 138°. Readily sol in water, solution turns yellow on exposure to air or light.

THERAP CAT: Antispasmodic.

5458. Lemon Peel. Outer rind of fresh ripe fruit of Citrus limonum (L.) Burm. f. C. medica var. limon L. f. Rutaceae. Habit: Northern India, cultivated in California, West Indies, Italy, Spain. Constit: Volatile oil, hesperidin, bitter principle.

USE: As a flavor in medicines, also in beverages, confectionery, and cooking.

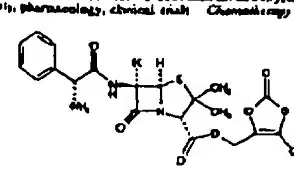
5459. Lenacil. 3-Cyclohexyl-6,7-dihydro-1H-cyclopentapyrimidine-2,4-(3H,5H)-dione; 3-cyclohexyl-5,6-trimethyleneuracil; 3-cyclohexyl-1,5,6,7-tetrahydro-2H-cyclopentapyrimidine-2,4(3H)-dione; Du Pont 634; Venzar. $C_{13}H_{18}N_2O_2$; mol wt 234.30. C 66.64%, H 7.74%, N 11.96%, O 13.66%. Prepn: S. Senda, H. Fujimura, Japan. pat. 63 6092 (1963); C.A. 59, 642g (1963), and herbicidal activity: B. J. Schwarzmeier, U.S. pat. 3,235,360 (1966 to du Pont Nemours). Synthesis: S. Senda et al., Chem. Pharm. Bull. 21, 1991 (1973). Mode of action: C. E. Hoffmann, Pestic. Chem., Proc. 2nd Int. Congr. Pestic. Chem. 5, A. S. Tahori, Ed. (Gordon and Breach Science Publishers, New York, 1972) pp 65-85. Soil metabolism: J. G. Wilton, W. E. Bray, Proc. 12th Brit. Weed Contr. Conf. 485 (1974). GC determn in soils: D. J. Gowdy, R. C. Dorsey, Analyst 102, 576 (1977). Soil persistence: M. Tomi et al., Weed Res. 23, 245 (1983). Field tolerance: D. V. Clay, Tests Agrochem. Cultiv. 11, 10 (1990).



Crystals from methanol or dioxane, mp > 290° (Senda, Fujimura). Also reported as light grey crystals from DMF, mp 310-315° (Schwarzmeier). Technical product properties: odorless, white to tan crystalline solid. d^{20} 1.32 kg/l. Vapor pressure (25°): 0.2 μPa. Solubility in water 6 mg/l, in xylene: 2 g/l. LD_{50} (80% wettable powder) orally in rats: > 11,000 mg/kg. LC_{50} 96 hr in Bluegill sunfish, rainbow trout: 100-1000, 135 mg/l. LC_{50} 8 day in bobwhite quail, Peking duck (mg/kg): 2300, > 5430 (DuPont technical data sheet).

USE: Herbicide.

5460. Lenampicillin. [2S-[2α,5α,6β(S*)]]-6-[(Aminophenylacetyl)amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl ester; ampicillin (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl ester; 6-[D(−)-α-aminophenylacetamido]penicillanic acid (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl ester. $C_{21}H_{23}N_3O_7S$; mol wt 461.51. C 54.65%, H 5.02%, N 9.11%, O 24.27%, S 6.95%. Orally active ampicillin prodrug. Prepn: F. Sakamoto et al., Eur. pat. Appl. 39,086; eidem, U.S. pat. 4,342,693 (1981, 1982 both to Kanebo); F. Sakamoto et al., Chem. Pharm. Bull. 32, 2241 (1984); S. Ikeda et al., ibid. 4316. Metabolism in man, dogs, rats: N. Arata et al., Japan. J. Antibiot. 38, 1776, 1785; C.A. 104, 161470a, 102550v (1985). Human pharmacokinetics: A. Saito, M. Nakashima, Antimicrob. Ag. Chemother. 29, 948 (1986). Series of articles on antibacterial activity, mutagenicity, pharmacology, clinical trials: Chemotherapy (Tokyo)

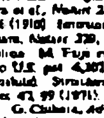


34, Suppl. 5, 1-933 (1986). Toxicity study: ... F. Ogura et al., ibid. 31.

Hydrochloride. $C_{21}H_{23}N_3O_7S.HCl$. KB-1585, KBT-1585; Takacillin, Varacillin. Crystals from isopropanol-ethyl acetate, mp 165° (dec). LD_{50} in male, female rats, male, female mice (mg/kg): approx 10000, approx 10000, 8294, 8497 orally; 4363, 4471, 1576, 4344 s.c.; 871, 838, 311, 775 i.v., 30 days (mg/kg). > 300 orally (Ogura).

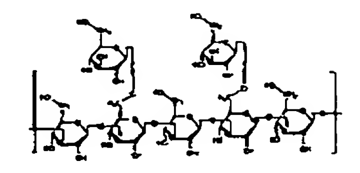
THERAP CAT: Antibacterial.

5461. Lenthionine. 1,2,3,5,6-Pentathiepane. $C_2H_4S_5$; mol wt 188.38. C 12.75%, H 2.14%, S 85.11%. Odorous principle from the edible mushroom Shiitake Lentinus edodes (Berk.) Sing. Isoln and synthesis: Morita, Kobayashi, Tetrahedron Letters 1966, 573. Simple, efficient synthesis: I. Still, G. W. Keirsey, Ibid 22, 1938 (1981).



Crystals from methylene chloride, mp 60-61°.

5462. Lentinan. LC-33. $(C_6H_{10}O_5)_n$; mol wt 400,000-800,000. Neutral polysaccharide isolated from the edible mushroom, Lentinus edodes (Berk.) Sing. Primary structure is a β-1,3-D-glucan having 2 β-1,6-glucopyranoside branchings for every 5 β-1,3 linear linkages. Isoln and antitumor activity: G. Chihara et al., Nature 222, 687 (1969); eidem, Cancer Res. 30, 2776 (1970). Immunostimulant activity: Y. Y. Maeda, G. Chihara, Nature 229, 634 (1971). Prepn of stable aqueous solutions: M. Fujii et al., Neth. pat. Appl. 7,801,916 corresp to U.S. pat. 4,207,312 (1976, 1980 both to Ajinomoto). Structural study: T. Sasaki et al., Carbohydr. Res. 47, 99 (1976). Preclinical evaluation and toxicity studies: G. Chihara, Adv. Exp. Med. Biol. 166, 189 (1983). Mechanism of action studies: H. Miyakoshi, T. Aoki, Int. J. Immunopharmacol. 6, 365, 373 (1984). Clinical trial in gastric and colorectal cancer: T. Taguchi et al., Adv. Exp. Med. Biol. 166, 181 (1983); K. Okuyama et al., Cancer 55, 2199 (1985). Review: G. Chihara, Int. J. Tissue Rea. 6, 207-225 (1983).



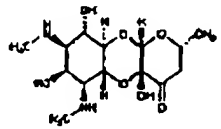
White powder, dec 250°. Sol in aqueous alkali, formic acid. Slightly sol in hot water, DMSO. Insol in cold water, alcohol, ether, chloroform, pyridine, hexamethylphosphoramide. Stable against sulfuric and hydrochloric acids. $[\alpha]_D^{20}$ +13.5-14.5° (in 2% NaOH), +19.5-21.5° (in 10% NaOH).

THERAP CAT: Antineoplastic, immunomodulator.

5463. Leonurine. 4-Hydroxy-3,5-dimethoxybenzoic acid 4-[(aminoiminomethyl)amino]butyl ester; 4-hydroxy-3,5-dimethoxybenzoic acid 4-guanidinobutyl ester; syringic acid 4-guanidinobutyl ester; [4-(4-hydroxy-3,5-dimethoxybenzoyloxy)butyl]guanidine; 4-guanidino-1-butanol syringate. $C_{14}H_{21}N_3O_5$; mol wt 311.34. C 54.01%, H 6.80%, N 13.50%, O 25.69%. Isoln from leaves of Leonurus sibiricus L., Labiatae: Kubota, Nakajima, C.A. 31, 773 (1936). Structure: Goto et al., Tetrahedron Letters 1962, 545. Revised structure: Kishi et al., ibid. 1968, 637. Structure and synthesis: Sugiura et al., Tetrahedron 25, 5155 (1969). Alternate synthesis: K. P. Cheng et al., Experientia 35, 571 (1979). Biological effect: H. W. Yeung et al., Planta Med. 31, 51 (1977).

and toxicology. Bupenthol et al. *J Pharmacol Exp Ther* 128, 210 (1957).
Liquid, bp$_{0.5}$ 185-195°.
Hydrochloride, $C_{16}H_{36}N_2O_2 \cdot HCl$, crystals from methanol + ether, mp 134-137°.
WARNING: Anticonvulsant.

6998. Spectinomycin. (3*R*-[3*a*,4*a*β,5*a*β,6*β*,7*β*,8*a*β,9*a*,9*a*β])-Decahydro-4*a*,7,9-trihydroxy-2-methyl-6,8-bis(methylamino)-4*H*-pyrano[2,3-*b*][1,4]benzodioxin-4-one; actinospectacin; oxyactinomycin; CNX-3100; M 461. $C_{14}H_{24}N_2O_7$; anol wt 332.35. C 50.59%, H 7.28%, N 8.43%, O 33.70%. Antibiotic isolated from fermentation broth of *Streptomyces spectabilis*: D. J. Mason *et al.*, *Antibiot & Chemother.* 11, 146 (1961); M. E. Bergy *et al.*, ibid. 661; M. H. Bergy, C. De Boer, U.S. pat 3,334,081 (1966 to Upjohn). Purification and crystallization: H. K. Jahnke, U.S. pat 3,384,540; V. J. Peters, U.S. pat 3,717,706 (1965, 1966 both to Upjohn). Isolation and characterization: A. C. Ruben, A. F. Wagner, *Antimicrob. Ag. Chemother.* 1963, 503. Structure: M. Hashimoto *et al.*, *J. Am. Chem. Soc.* 84, 3213 (1962); P. F. Wiley *et al.*, ibid. 85, 2032 (1963). Solubility data: J. R. Mann, P. J. Wren, *J. Assoc. Offic. Anal. Chem.* 50, 437 (1967). Biochemistry and site study: T. G. Cochran *et al.*, *Chem. Commun.* 1972, 494. Biosynthesis: L. A. Mitscher *et al.* ibid. 1973, 1341; M. Davies *et al.*, *J. Am. Chem. Soc.* 857, 5817 (1985). Enantiomeric synthesis: D. B. White *et al.*, *Tetrahedron Letters* 29'28, 2757. S. Hanessian, R. Roy, *Can. J. Chem.* 63, 363 (1985). Mechanism of action study: M. T. Brink *et al.*, *Biochim. Biophys. Acta* 23, 325 (1994). HPLC detection in animal plasma: N. Haagsma *et al.*, *J. Chromatog.* 615, 289 (1993). Clinical pharmacokinetics: J. G. Wagner *et al.*, *Int. J. Clin. Pharmacol. Ther. Toxicol.* 1, 261 (1968). Clinical evaluation in gonorrhea: V. N. Kanti *et al.*, *Gastroenterol. Med.* 65, 340 (1968); in chancroid: M. Ouassis *et al.*, *Soc. Trauma. Dis.* 19, 291 (1977). Co-treatment with Lincomycin, *q.v.*, *Int. Journal in chemo*: C. M. Vanning *et al.*, *Aust. Vet. J.* 47, 256 (1980). Review: W. M. McCormack, M. Finland, *Ann. Intern. Med.* 64, 717-715 (1976); W. J. Holloway, *Med. Clin. North Am.* 66, 169-173 (1982).



Amorphous powder, $[\alpha]_D^{25}$ −20° (water). pK_{a1} 6.95, pK_{a2} 8.70. Sol in water, methanol, ethanol. Insol in acetone, hydrocarbon solvents.

Dihydrochloride pentahydrate, $C_{14}H_{24}N_2O_7 \cdot 2HCl \cdot 5H_2O$. *Synonyms:* Spectogard, Stanilo, Togamycin, Trobicin, Trobicin. Exists as a trigonal hydrate and not as the carbonyl form (Cochran *et al.*). Colorless needles from aq methanol, mp 204-207° (dec). $[\alpha]_D$ +34.8° (c = 0.42 in water). Sol in water, methanol, propylene glycol, formamides. DMSO, 0.1N NaOH, 0.1N HCl: > 20 mg/ml. Sol (mg/ml): chloroform 0.001, acetone 0.015, diethyl ether 0.010.

Sulfate tetrahydrate, $C_{14}H_{24}N_2O_7 \cdot H_2SO_4 \cdot 4H_2O$, white crystals from aq acetone, mp ~185° (dec). $[\alpha]_D^{25}$ +177.5° (c = 1 in water). pK_{a1} 1.00, pK_{a2} 2.73. Sol: in water, DMSO 23.3, 9.15 (mg/ml). Practically insol in pyridine, chloroform, ethanol, ethyl acetate, cyclohexane, benzene, acetone, DMF, dioxane, carbon tet.

THERAP CAT: Antibacterial.
THERAP CAT PROD: Antibacterial.

6999. Spectrin. Talkin A. Major protein component of the membrane cytoskeleton of mammalian and avian erythroid cells. Responsible for maintaining the normal shape, strength and stability of the erythrocyte. A ubiquitous family of proteins, spectrin analogs have also been isolated from a variety of nonerythroid cells. Given the name spectrin because of its original isolation from hemoglobin-free cell membranes known as erythrocyte "ghosts": V. T. Marchesi, E. Steers, *Science* 159, 203 (1968). Comparison with actin, *q.v.*: E. Steers, V. Marchesi, *J. Gen. Physiol.* 61, 65 S (1969). Cells from human red cells and various comparison: T. W. Tillack *et al.*, *Biochim. Biophys. Acta* 300, 125 (1970). Spectrin is a heterodimer composed of 2 high and not polypeptide subunits referred to as band 1 or α-spectrin (mol wt ~240 kDa) and band 2 or β-spectrin (mol wt ~220 kDa). Structural studies: M. Clarke, *Biochim. Biophys. Res. Commun.* 45, 706 (1972); T. L. Steck, *J. Cell Biol.* 62, 1 (1974); J. M. Anderson, *J. Biol. Chem.* 254, 1377 (1979); D. W. Speicher *et al.*, *ibid.* 258, 9307 (1983). The presence of spectrin is found to be the red cell membrane by proteins known as ankyrin: V. Bennett, P. J. Stenbuck, *ibid.* 254, 2533 (1979), or syndesmos: J. Yu, S. H. Goodman, *Proc. Nat. Acad. Sci. USA* 76, 2340 (1979). The spectrin heterodimers aggregate on the membrane surface and, together with actin and other proteins, form a filamentous network that covers the surface of the cytoplasmic membrane: S. E. Lux, *Nature* 281, 426 (1979); *idem, Ann. Hematol.* 36, 21 (1979). Identification of spectrin analogs from nonerythroid cells: S. R. Goodman *et al.*, *Proc. Nat. Acad. Sci. USA* 78, 7570 (1981). Lack of fodrin, also known as brain or neural cell spectrin: J. Levine, M. Willard, *J. Cell Biol.* 90, 631 (1981); V. Bennett *et al.*, *Nature* 299, 126 (1982). Lack of TW 260/240, a spectrin analog from chicken intestinal epithelial cells: J. R. Glenney *et al.*, *Cell* 28, 843 (1982). Comparison of erythroid and nonerythroid spectrin: J. R. Glenney, *J. Biol. Chem.* 258, 7180 (1983); J. R. Glenney, P. Glenney, *Eur. J. Biochem.* 144, 539 (1984). Review of erythrocyte spectrin: S. R. Goodman, K. Shiffer, *Am. J. Physiol.* 244, C121-C131 (1983), and several cell spectrins: S. R. Goodman, I. S. Zagon, *ibid.* 284, C307-C320 (1983). Comprehensive review: S. R. Goodman *et al.*, *Crit. Rev. Biochem.* 23, 171-234 (1988).

6991. Spermaceti. Cetaceum. Synonyms: A waxy substance from the head of the sperm whale, *Cetus*. Chiefly cetyl palmitate, but cetyl alcohol present in appreciable amounts; esters of lauric, stearic, and myristic acids, esters of higher alcohols also present.

White, semicrystalline translucent, slightly unctuous mass with crystalline fracture and pearly luster, almost odorless and tasteless but becomes yellow and rancid on long exposure to air. d 0.935-0.944, mp 42-50°, n_D^{60} ~1.4300. Saponification no. 120-136, iodine no. 3-14. Used in waxes or cold cream. Sol in chloroform, ether, carbon disulfide, oils, boiling alcohol, slightly sol in cold ether.

USE: As a base for ointments, creams, etc., and as emulsions with egg yolk or expressed almond oil. In waxed candles, soaps, cosmetics, laundry wax, finishing and lustering. Emollient.

6992. Spermidine. *N*-[3-Aminopropyl]-1,4-butanediamine, *N*-(3-aminopropyl)tetramethylenediamine; $C_7H_{19}N_3$; mol wt 145.25. C 57.89%, H 13.18%, N 28.93%. $NH_2(CH_2)_3NH(CH_2)_4NH_2$. Biogenic polyamine formed from putrescine, a precursor of spermine, *q.v.* First detected in human sperm, but occurs widely in nature. Essential for both normal and neoplastic tissue growth. Synthesis: H. W. Dudley *et al.*, *Biochem. J.* 28, 1063 (1934); 31, 97 (1937); J. V. Braun, W. Yanicopulo, *Ber.* 70, 1234 (1937); M. Bergmann, H. F. Schiele, *J. Am. Chem. Soc.* 74, 1836 (1937). For reviews of the early literature see N. Campbell, *Die Enzymatische Aktivität* (S. Karger, Basel, 4th ed., 1952) 619 pp; H. Tabor *et al.*, *Ann. Rev. Biochem.* 30, 579-604 (1961). Role on cell growth processes: C. W. Tabor, H. Tabor, *Adv. Enzymol.* 41, 113 (1976); *J. Biol. Chem.* 251, 5261 (1976); *Biochim. Biophys. Acta* 473, 181 (1976); C. W. Porter, R. J. Bergeron, *Science* 219, 551 (1983). Formation and interconversion of spermidine and putrescine in mammalian cells: A. E. Pegg *et al.*, *Adv. Enzyme Regul.* 19, 427 (1980). Effect on polypeptide chain elongation in vitro: A. K. Abraham, A. Hild, *Eur. J. Biochem.* 106, 357 (1980). Regulation of tRNA methylase kinase activity: M. Mosbach *et al.*, *Biochem. J.* 207, 153 (1982). HPLC study: C. E. Pramell, D. M. Russell, *J. Chromatog.* 239, 61 (1982). Interactions with actin, *q.v.*: C. Orrell-Andre, *Biochim. Biophys. Res. Commun.* 106, 1096 (1982). Studies as an aid in biochemical tool in cancer research: A. Thys *et al.*, *Bull. Cancer Clin. Oncol.* 69, 611 (1982); V. Gerencser *et al.*, *J. Biol. Chem.* 257, 8068 (1982); C. W. Tabor *et al.*, *J. Am. Chem. Soc.* 82, 4812 (1983). Toxicity study: P. A. Lang, *Toxicol. Lett.* 17, 195-203 (1983). Review: T. C. Thatcher, *Life Sci.* 27, 707-713 (1980); O. Heby, *Differentiation* 19, 1-20 (1981); L. Infantosi, *Med. Biol.* 60, 306-313 (1982). Book: *Polyamines in Biology and Medicine*, D. R. Morris, L. J. Marton, Eds. (Dekker, New York, 1981) 517 pp.

Liq, bp$_{10}$ 126-130°. Sol in water, ethanol, ether.

Tetrahydrochloride, $C_7H_{19}N_3 \cdot 4HCl$, crystal from ethanol + HCl, mp 258-259°.

USE: As a tool in biochemical research.

6994. Spermine. *N,N'*-Bis(3-aminopropyl)-1,4-butanediamine, *N,N'*-bis(3-aminopropyl)tetramethylenediamine, putrescine, mycoludamine, norspermine; $C_{10}H_{26}N_4$; mol wt 202.34. C 59.36%, H 12.95%, N 27.69%. $H_2N(CH_2)_3NH(CH_2)_4NH(CH_2)_3NH_2$. Biogenic polyamine formed from spermidine, *q.v.*, and occurring in almost all tissues. Essential for both normal and neoplastic tissue growth. First observed in human semen and described as the crystalline phosphate salt by A. von Leeuwenhoek, *Phil. Trans. Roy. Soc. London* 12, 1040 (1674). For a description of the dietary occurrence, formation, and early proofs of spermine, see *Salmon* vol. IV, Suppl. I, 704; M. Guggenheim, *Die Stoffe Amine* (S. Karger, Basel, 4th ed., 1951) 619 pp; H. Tabor *et al.*, *Ann. Rev. Biochem.* 30, 579-604 (1961). Proof of structure and its tetrabenzochloride: Ernst *et al.*, *J. Med. Chem.* 7, 710 (1964). Role in cell growth processes: C. W. Tabor, H. Tabor, *Ann. Rev. Biochem.* 45, 285 (1976); *J. Gen. Appl. Microbiol. Biochim. Biophys. Acta* 473, 181 (1978). Modulator of calcium-dependent exocytic processes: T. C. Theoharides, *Life Sci.* 31, 1703 (1982). Biosynthesis in fungi: J. Stuart, *Med. Biol.* 59, 304 (1981). HPLC study: C. E. Pramell, D. M. Russell, *J. Chromatog.* 239, 47 (1982). Use as a biochemical marker for malignant tumors: V. Ilievski *et al.*, *Cancer Res.* 43, 3246 (1983). Metabolic study: A. E. Pegg *et al.*, *Biochemistry* 21, 3063 (1982). Review of role in cell proliferation and differentiation: O. Heby, *Differentiation* 19, 1-20 (1981). Book: *Polyamines in Biology and Medicine*, D. R. Morris, L. J. Marton, Eds. (Dekker, New York, 1981) 512 pp.

Needles, mp 34-60°. Liq, bp$_{760}$ 151-152°. Strong base. Absorbs carbon dioxide from air. Keep well closed. Sol in water, lower alkanols, chloroform. Practically insol in ether, benzene, petr ether.

Diphosphate (tetrahydrate), $C_{10}H_{26}N_4O_8P_2 \cdot 4H_2O$, *synonyms:* phosphate. Crystal from water, mp 230-234° (dec). Solubility in water 0.0376 at 20°, 1% at 100°. Insol in alc, ether and other organic solvents. Sol in dilute acids and alkali. Known as Charcot-Neumann crystals, also found in sputum, blood, bone marrow in leukemia and secretions in asthma.

Tetrahydrochloride, $C_{10}H_{26}Cl_4N_4$, crystal from ethanol, mp 313-315°.

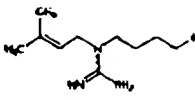
USE: As a tool in biochemical research.

6995. Sperm Oil. From sperm whale. *Cetus*. Esters of fatty acids, small quantities of spermaceti.

Yellow, thin liquid, slight fishy odor; it acts as good quality. d 0.875-0.884. Saponification no. 123-147, iodine no. 68-84. Insoluble in water, cold alcohol, in petr ether; sol in chloroform, ether.

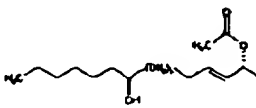
USE: As lubricant, in lotions, hardening steel, mineral soap.

6996. Sphaeroplasine. *N*-(4-Aminobutyl)-*N*-[2-methylol-2-hydroxymethyl-4-butanediamine, 4-sphaeroplasine; $C_{10}H_{24}N_4$; mol wt 184.31. C 65.17%, H 13.15%, N 30.25%. Obtained from the following Central Asiatic leguminous *Sternbergia colchiciflora* (Pall.) Trev. (*Sphaeroplasis colchiciflora* (Pall.) DC.). Seeds contain various bases. Separation: Levi, Rubashkin, Mandelbaum, *J. Gen. Chem. USSR* 14, 761 (1944); Rybchenko, *ibid.* 11, 2365 (1947); Malik, *ibid.* 23, 347 (1953). Structure: Hesse, Leistner, *Liebigs Ann.* 703, 214 (1970).



Strong, caustic base.
Dibenzoate, $C_{24}H_{36}N_4O_4$, crystals, mp 149-150°.

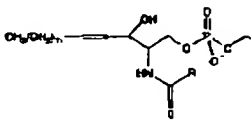
6997. Sphingomyelins. Family of six antifungal agents, sphingolipsins A-F, isolated from *Aspergillus fumigatus* of which sphingolipsin C is the most abundant. Specific inhibitors of serine palmitoyltransferase. Isolation and characterization of sphingolipsins A-D: P. VanMiddlesworth *et al.*, *J. Antibiot.* 45, 661 (1992). *N*-stearoyl analogue: F. W. S. Hoon *et al.*, *Biol. Mass Spectrometry* of A-D: P. VanMiddlesworth *et al.*, *Tetrahedron Letters* 33, 297 (1992). Mechanism of action: M. M. Zweerink *et al.*, *J. Biol. Chem.* 267, 25033 (1992). Synthesis of D: K. Mori, K. Ebata, *Tetrahedron Letters* 35, 9207 (1994).



Sphingolipsin C

Sphingolipsin C, $C_{21}H_{41}NO_4$, 3-keto-(2*S*,4*R*)-2-amino-1,4-dihydroxy-6-octadecene, crystal, colorless solid.

6998. Sphingomyelins. Ceramidecholine. Sphingolipid phosphatides occurring in the myelin sheaths of animal tissues of beef heart sphingomyelin. Reviews: *Lipmann, J. Biol. Chem.* 182, 63 (1950). Lipids from human and rat brain: Mandoker *et al.*, *Nat. Chim. Acta* 46, 601 (1967); Structure: Fujino, *J. Biochem. (Japan)* 59, 45 (1952); Rouser *et al.*, *J. Am. Chem. Soc.* 73, 310 (1951); Maniscalco *et al.*, *ibid.* 313. Structure of beef-brain *(Ann methyl)* sphingomyelin: Kanfmann *et al.*, *Biochim. Biophys. Acta* 270, 113 (1972). Synthesis of dihydrosphingomyelins: Shapiro *et al.*, *J. Am. Chem. Soc.* 80, 2339 (1958). Synthesis of sphingomyelins: Shapiro *et al.*, *ibid.* 81, 3743, 4050 (1959). Constituents: Shapiro, *Flowers, Ind.* 84, 1047 (1962). Monograph: S. R. Kasey, *The Biology of Lipids* (Interscience-Wiley, New York, 1959).



R = fatty acids such as stearic, palmitic, lignoceric, nervonic acids.

Slightly hygroscopic powder. Occurs as a hydrate. Sol in hot aqueous alcohol, acetic acid, chloroform; slightly sol in ether, acetone, water.

6999. Sphingosine. (*R*)-2-Amino-(*E*)-4-octadecene-1,3-diol; (*E*)-2-amino-4-octadecene-1,3-diol; 1,3-dihydroxy-2-amino-4-octadecene, 4-sphingenine; $C_{18}H_{37}NO_2$; mol wt 299.50. C 71.19%, H 12.39%, N 4.68%, O 10.68%. Important membrane component, long-chain amino-dialcohol, moiety of many phosphatides, such as sphingomyelins, cerebrosides, and gangliosides. Natural sphingosine is (*R*)-(+)-erythro-2,3-dihydroxy-2-amino-4-trans-octadecene. Does not exist in the free state in animals, plants or microorganisms. First obtained by hydrolysis of cerebrosides from brain: J. L. W. Thudichum, *Die Konstitution des Gehirns des Menschen und der Tiere* (Tübingen, 1901). Separation procedure: Carter *et al.*, *J. Biol. Chem.* 210, 249

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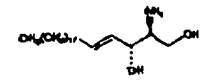


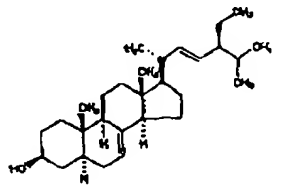
DL-Sphingosine, waxy crystals from ether + pentane, mp 67°.

DL-Tetradecylsphingosine. $C_{32}H_{67}NO_2$, crystals from pentane + ether, mp 91-92°.

Tetradecyl dicrotonine of natural sphingosine. $C_{46}H_{85}NO_4$, crystals, mp 101-102°, $[\alpha]_D^{25}$ −11.7° (chloroform).

8900. Spigelia. Pinkroot, Indian pink, Carolina pink, Maryland pink, wormgrass. Dried rhizome and roots of *Spigelia marilandica* L., Loganiaceae. Habit: North American (New Jersey to Florida and west to Wisconsin). Cinnamic, Spigelinic, resin, tannin, bitter principle, volatile oil.
THERAP CAT: Anthelmintic.

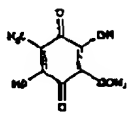
8901. α-Spinasterol. 11*H*,5α,7*H*,22*E*)-Stigmasta-7,22-dien-3-ol; α-spinasterin; beta-sitosterol, hydrate of $C_{29}H_{48}O$, mol wt 412.70. C 84.40%, H 11.72%, O 3.88%. Purified by repeated crystallization with chloroform-methanol, g.v. Extracted from spinach leaves. Haul, Heyl, *J. Biol. Chem.* 99, 511 (1932), from *Corylus rostrata* Schrad., Corylaceae. Hamilton, Kornacki, *J. Am. Chem. Soc.* 1952, 5011. Structure: Fieser *et al.*, *J. Am. Chem. Soc.* 71, 2226 (1949). Proper Rancho, Beaverton, *J. Org. Chem.* 38, 2259 (1973). IR: Amiantin *et al.*, *J. Chem. Soc. Perkin Trans. 1* 1981, 3366.



Crystals from alcohol + light petr, mp 166-169°. $[\alpha]_D^{25}$ −2.6° (c = 2.8 in chloroform)

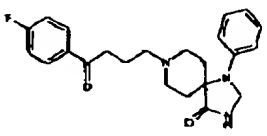
Benzoate, $C_{36}H_{52}O_2$, plates from ethyl acetate, mp 207°. $[\alpha]_D^{25}$ +1.6° (c = 1.7 in chloroform).

8902. Spiradiolone. 2,5-Dihydroxy-3-methoxy-6-methyl-2,5-cyclohexadiene-1,4-dione; 2,5-dihydroxy-3-methoxy-6-methyl-*p*-benzoquinone; 3,6-dihydroxy-5-methoxy-*p*-toluquinone; 3,6-dihydroxy-4-methoxy-2,5-toluquinone; hydroxyfumigatin. $C_8H_8O_5$; mol wt 184.15. C 52.18%, H 4.38%, O 43.44%. Metabolic product of the fungi *Penicillium spiculisporum* Thom and *Aspergillus fumigatus* Fres.: Birkinshaw, Raistrick, *Philos. Trans.* B230, 345 (1939); Anslow, Raistrick, *Biochem. J.* 32, 2286 (1938). Petersen, *Acta Chem. Scand.* 27, 1771 (1973). Structure: Anslow, Erdtman, *Svensk Kem. Tidskr.* 48, 208 (1937). Synthesis: Anslow, Raistrick, *Biochem. J.* 32, 800 (1938). Biosynthesis: Petersen, *Acta Chem. Scand.* 23, 1046 (1969).



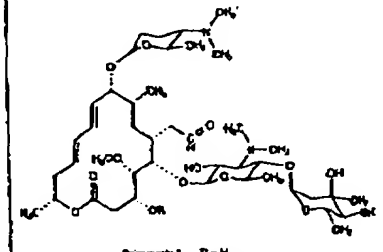
Pumpkin-black crystals, mp 287°. Slightly sol in cold water, more sol in hot water, sol in dil NaOH with a strong purple color with a bluish hue.

8903. Spiperone. 8-[4-(4-Fluorophenyl)-4-oxobutyl]-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one; 8-[γ-(*p*-fluorobenzoyl)propyl]-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one; 4-phenyl-8-[4-(*p*-fluorobenzoyl)propyl]-1-oxo-3,4,8-triazaspiro[4.5]decane. Spiroperidon. $C_{23}H_{26}FN_3O_2$, mol wt 395.48. C 69.85%, H 6.63%, F 4.80%, N 10.63%, O 8.09%. Prepn: Janssen, U.S. pats 3,155,669; 3,155,670 and 3,161,644 (all 1964 to Janssen).



Crystals, mp 198-203°.
THERAP CAT: Antipsychotic.

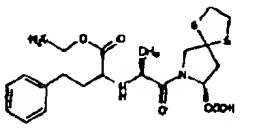
8904. Spiramycin. RP-5337; Selectomycin; Rovamycin. Antibiotic substance classified in the oxytetracycline-erythromycin group and produced by *Streptomyces ambofaciens* from soil of northern France: Grasso *et al.*, *Compt. Rend. Soc. Biol.* 234, 1491 (1952); Pinnert-Sindico *et al.*, *Antibiot. Ann.* 1954-1955, 734. Nmr: Verma, US pat 3,843,633 (1960 to Rhône-Poulenc); see also US pat 3,000,785 (1961 to Rhône-Poulenc). Antibacterial activity and toxicity: H. Saw *et al.*, *Antibiotics Chemother.* 6, 366 (1956). Separation into 3 components, as acid epoxy salts I, II and III: Pinnert-Sindico, Charpentier, US pats 2,916,480 and 3,031,447 (1961 to Rhône-Poulenc). Structure: Keller-Juslen, Bormann, *J. Am. Chem. Soc.* 87, 4660 (1965). Revised structure: Omura *et al.*, *Med.* 91, 3401 (1969). NMR: Gibbons *et al.*, *J. Antibiot.* 26, 55 (1973). Revised configuration at C-9: Tadanier *et al.*, *J. Org. Chem.* 39, 3474 (1974). Symposium on pharmacology, antibacterial spectrum, and clinical efficacy: *J. Antimicrob. Chemother.* 2, Suppl. B, 1-213 (1976).



Spiramycin I R = H
Spiramycin II R = $COCH_3$
Spiramycin III R = $COCH(CH_3)_2$

Amorphous base, slightly sol in water. $[\alpha]_D^{25}$ −92° (methanol); uv max (ethanol): 231 nm. Sol in most organic solvents. Active on gram-positive bacteria and rickettsiae. Cross resistance between microorganisms resistant to erythromycin and carbomycin. LD_{50} in rats (mg/kg): 9400 orally, 8400 s.c., 790 i.v. (Selectomycin).
Veterinary: Spira 300.
Homologues, *spiramycin adjuncts*, *Stilamycins*, *Selomycin*: *Spiramycin I*, $C_{43}H_{74}N_2O_{14}$. *Foromacidin A*. Crystals, mp 134-137°. $[\alpha]_D^{25}$ −76°.
Spiramycin II (acetate). Crystals, mp 140-142°. $[\alpha]_D^{25}$ −97.5°.
Spiramycin III, $C_{45}H_{76}N_2O_{15}$. *Foromacidin B*. Crystals, mp 130-133°. $[\alpha]_D^{25}$ −85°.
Spiramycin IV (diacetate). crystals from cyclohexane, mp 158-160°. $[\alpha]_D^{25}$ −98.6°.
Spiramycin VII, $C_{47}H_{78}N_2O_{15}$. *Foromacidin C*. Crystals, mp 126-131°. $[\alpha]_D^{25}$ −83°.
Spiramycin VII (diacetate). crystals from cyclohexane, mp 140-142°. $[\alpha]_D^{25}$ −99.4°.
THERAP CAT: Antibacterial.
THERAP CAT (vet): Antibacterial; growth promotant.

8905. Spiraprilat. (4*S*-[1[*R**,3*R**(*R**)],4*R**]]-3-[2-[1-Ethoxycarbonyl-3-phenylpropyl]amino]-1-oxopropyl]-1,4-dithia-7-azaspiro[4.4]nonane-2-carboxylic acid; (4*S*)-7[*S*]-*N*-[(*S*)-1-carboxy)-3-phenylpropyl]-alanyl]-1,4-dithia-7-azaspiro[4.4]nonane-2-carboxylic acid, ethyl ester. $C_{25}H_{36}N_2O_6S_2$, mol wt 444.62. C 54.67%, H 6.45%, N 6.00%, O 17.64%, S 13.24%. Angiotensin-converting enzyme (ACE) inhibitor. Prepn: E. M. Gold *et al.*, U.S. pat 4,470,972 (1984 to Schering); E. M. Smith *et al.*, *J. Med. Chem.* 31, 1560 (1988). Pharmacology: E. J. Sybertz *et al.*, *Arch. Int. Pharmacodyn. Ther.* 284, 214 (1987); T. Baum *et al.*, *Ibid.* 290 Supplementary issue, 224 (1987); M. Hannon-Nix *et al.*, *Prev. Drug Metab.* 14, 224 (1990). Pharmacokinetics and evaluation in CHF: S. A. J. van den Meiracker *et al.*, *J. Cardiovasc. Pharmacol.* 16, 614 (1990). Clinical evaluation in essential hypertension: G. P. Rosati *et al.*, *J. Clin. Pharmacol.* 31, 348 (1991). *Review*: W. Jain, H. J. Krause, *Cor Vasa* 34, 83-91 (1992).



Hemihydrate, white foam. $[\alpha]_D^{25}$ −29.5° (c = 0.2 in ethanol).
Hydrochloride. $C_{25}H_{36}N_2O_6S_2 \cdot HCl$. *Soft Ribbet, Tri-Ritz, Rimarace, Empress, Leadpril*. White solid, mp 182-184° (dec). $[\alpha]_D^{25}$ −13.7° (c = 0.4 in ethanol).
Benzil. $C_{27}H_{34}N_2O_5S_2$, *spiraprilat, spiraprilic acid*, Sch-33961. Monohydrate, mp 143-145° (dec). $[\alpha]_D^{25}$ +41° (c = 0.4 in ethanol).
THERAP CAT: Antihypertensive.

8906. Spirit of Ammonia, Aromatic. Spirit of hartshorn, aromatic. A soln contg 31 g ammonium carbonate, 10 ml 18% ammonia water, 10 ml lemon oil, 1 ml oil of lavender, 1 ml oil of myristica, 700 ml alcohol and a sufficient quantity of water to make 1 liter. Absolute alc by vol. ~44%.
Almost colorless to slightly yellow liquid with an aromatic, pungent odor and the taste of ammonia. d 0.90. Forms an opalescent mixture with water, miscible with alcohol.
THERAP CAT: Edible respiratory stimulant.
THERAP CAT (vet): By inhalation: respiratory and circulatory stimulant. Internally: expectorant, diaphoretic, antacid, carminative. Externally: counterirritant, and as dilutant to relieve the irritation of insect stings and bites.

8907. Spirit of Camphor. A soln of camphor in alcohol contg 10 g camphor per 100 ml soln.
Colorless liquid, camphor odor.
THERAP CAT: Carminative, analgesic (topical), antipruritic.
THERAP CAT (vet): Has been used as rubefacient, stimulant, expectorant, carminative.

8908. Spirit of Chloroform. An alcoholic soln of chloroform contg 9% by vol of chloroform, corresponding to 10.5% by wt, and ~91% abs alcohol by vol.
Colorless, clear liquid, chloroform odor. d ~0.85.
THERAP CAT: Carminative.

8909. Spirit of Ether. Hoffmann's Drops. A mixture of alcohol and ether. Made by mixing 325 ml ether U.S.P. with sufficient U.S.P. alcohol (~690 ml) to make 1000 ml. Absolute alc by vol. ~66%.
Colorless, volatile liquid. d 0.785.
THERAP CAT: Carminative.

8910. Spirit of Ether Compound. Hoffmann's anodyne. A mixture of 333 ml ether U.S.P., 25 ml ethanol and sufficient alcohol (~665 ml) to make 1000 ml. Absolute alc by vol. ~68%.
Colorless, clear liquid. d ~0.785.
THERAP CAT: Carminative.
THERAP CAT (vet): Has been used as a stimulant, carminative, tonic.

8911. Spirit of Ethyl Nitrite. Spirit of nitrous ether, sweet spirit of nitre. An alcoholic soln of ethyl nitrite, usually 3.5-4.5% ethyl nitrite. Incompat: Antipyrine, tannin, acetanilide, acetophenetidin, iodides, tincture guaiac, morphine salts, carbenzin, arazine.
Pale yellow or faintly greenish-yellow, clear, mobile, volatile, flammable liquid, ethereal fungal odor, sharp burning taste. The ethyl nitrite evaporates rapidly, decomposes to air, esp in light. d not above 0.823 at 15°. Miscible with water and alcohol. *Keep tightly closed protected from light in a cool place, remote from fire.*
THERAP CAT: Diaphoretic, diuretic.

8912. Spirit of Formic Acid. Spirit of acid. Composed of 40 ml of 75% formic acid and 335 ml water or sufficient alcohol to make one liter; corresponds to ~4% formic acid and ~70% abs alcohol by vol.
Colorless liquid. Miscible with water, alcohol.

8913. Spirit of Glyceryl Trinitrate. Spirit of trinitroglycerin, spirit of nitroglycerin, spirit of glonoin, soln of glyceryl trinitrate. An alcoholic soln contg 1.0 ± 1% glyceryl trinitrate. *Incompat*: Alkalies, carbonates. HCl. IHP.
Colorless, clear liquid. d 0.814-0.820. Miscible with alcohol, chloroform, ether, 1 ml dissolves in 6 ml almond oil; very slightly sol in water, miscible with chloroform, ether.
Caution: Likely to produce violent headache when taken or applied to the skin.
Note: When spilled, immediately pour NaOH soln over it or dry residue may explode by friction or shock.
THERAP CAT: Vasodilator.

8914. Spirit of Peppermint. An alcoholic soln, containing 3 to 5 ml of peppermint and the alcohol-soluble principles from 10 g of powdered peppermint previously macerated with water.
THERAP CAT: Carminative.
THERAP CAT (vet): Has been used as a carminative.

8915. Spirit of Spearmint. An alcoholic soln contg per liter 100 ml oil of spearmint and the alcohol-soluble principles from 10 g coarsely powdered spearmint leaves previously macerated with water.
THERAP CAT: Carminative.
THERAP CAT (vet): Has been used as a carminative.

8916. Spirogermanium. 4,8-Dimethyl-*N*,*N*-dimethyl-1-oxa-4-germaspiro[4.5]decane-3-propanamine; 2-[3-(dimethylaminopropyl)-8,8-dimethyl-2-oxa-8-germaspiro[4.5]decane $C_{15}H_{32}GeN_2O$, mol wt 345.18. C 59.86%, H 10.64%, Ge 21.59%, N 8.21%. Cytostatic germanium dioxide. Preps: L. M. Rice, Ger. pat 2,343,568, *eidem*, U.S. pat 3,813,406 (1972, 1974 both to Geochemical Fund for Med. Res.); L. M. Rice *et al.*, *J. Heterocycl. Chem.* 11, 1041 (1974). Preclinical toxicological evaluation: M. C. Henry, C. D. Port, *U.S. NTIS Rep. PB-244 873* (1977) 213 pp.; *CA* 87, 177830 (1977). Early clinical studies: F. S. Schnee *et al.*, *Chemotherapy Rep.* 64, 1051 (1965); C. Trapé *et al.*, *Ibid.* 66, 15 (1911). Toxicity study: M. C. Henry *et al.*, *Ibid.* 64, 1317 (1910).